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*Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia*

By W. B. CASTLE (by invitation) and EDWIN A. LOCKE, Boston, Mass.

The action of liver in benefiting cases of pernicious anemia promptly and throughout the duration of the liver diet suggests the possibility of a deficiency etiology for the disease. The deficiency would, however, seem not to be of the usual dietary type, for liver is ordinarily absent from the diet of unaffected normals. The high incidence of a marked reduction of hydrochloric acid and pepsin in the stomach, sometimes discovered before the development of the disease, and not affected by the general improvement of the patient on a liver diet, suggests that the achylia may possibly play an intermediary rôle in causing the deficiency. An obvious possibility, especially in view of the probable polypeptid nature of the effective principle in liver extract, is a deficiency of the gastric digestion of protein.

To test this idea, the contents of the stomach of a normal man recovered one hour after a meal of 300 grams of rare Hamburg steak was administered daily to each of ten patients with pernicious anemia. The material as obtained from the normal stomach was treated with strong hydrochloric acid to pH 2 to 3, incubated six hours, then neutralized with sodium hydroxide to pH 5, and given by stomach tube to the fasting patient. In eight of the ten patients so treated clinical improvement, a characteristic rise of the reticulocytes and a progressive increase of the red blood cells was observed, comparable to effects ordinarily seen with small doses of liver in similar patients. In one of the eight cases benefited the effect may have been initiated by a transfusion, and in one of the two cases showing no clinical improvement there was a slight increase in the reticulocytes at the expected time.

The daily administration of mixtures of 300 grams of Hamburg steak with commercial pepsin or with 150 grams of the mucous membrane of the pig's stomach, incubated like the gastric contents, was found ineffective in three of these ten cases, and in two others. In three cases of this series, and in two other cases 200 to 300 grams of Hamburg steak daily were given without effect. In another case, mixtures of Hamburg steak and hydrochloric acid gave no benefit. In view of Elders' work these controls must nevertheless be multiplied.

At present a definite conclusion is impossible, but these observations suggest that the secretions of the normal gastric mucous membrane alone, or through their action on food proteins, can produce some substance capable on oral administra-

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*The Effect of Hyperthyroidism on the Total Blood Count* By HARRY BLOTNER, REGINALD FITZ, and WILLIAM P. MURPHY, Boston, Mass

A few years ago Thompson showed that the plasma volume is diminished in myxedema. We attempted to study the converse of his work by studying the plasma volume in hyperthyroidism. We at once became interested in the behavior of the red cell count. It appeared that the ordinary method for counting red cells is relatively inaccurate, the blood count is expressed in corpuscles per volume of blood without taking into consideration differences in total blood volume which may occur, or differences in individual body size and shape. We made, therefore, total red blood counts expressed in trillion red cells circulating per square meter of surface area. When so expressed, patients with a low metabolic rate appear to have a low total red blood count which increases in almost direct proportion to an increasing metabolic rate. Patients with hyperthyroidism have a high total red count. The rising total red count which parallels a rising metabolic rate in thyroid disorders is very similar to the rising red count found in pernicious anemia cases under treatment with liver. It appears, therefore, that the rate of metabolism may have an appreciable effect upon the total red count. Our data bring to mind the possibility that the factor of stimulation of the metabolism of the blood forming tissues may be one possible factor in the beneficial effect of liver in pernicious anemia, although before this point can be particularly stressed, further observations are necessary.

*The Chloride, Base and Nitrogen Content of Gastric Juice After Histamine Stimulation* By W. SCOTT POLLAND and A. M. ROBERTS (by invitation) and A. L. BLOOMFIELD, San Francisco, Calif

See published article, *JOUR. CLIN. INVEST.*, 1928, v, 611

*Histologic Studies on the Small Peripheral Arteries and Arterioles in Ambulatory Cases of High Blood Pressure* By J. W. KERNOHAN and E. W. ANDERSON (by invitation), and N. M. KEITH, Rochester, Minn

Tissues taken at autopsy from cases of malignant hypertension showed, as the significant histologic picture, a diffuse arteriolar lesion. This suggested further study of the smaller vessels in tissue obtained from ambulatory patients with high blood pressure. The biopsy material was obtained from the pectoral muscle. The histologic study of the arterioles in this tissue form the basis of this report. All cases show marked thickening of the walls of the smaller arteries and arterioles, especially hypertrophy of the muscular elements of the media and also hypertrophy of the internal elastic lamina. Pervascular fibrosis is not constant. There seem to be different degrees of hyperplasia of the lining endothelium of these vessels but the hyperplasia is not particularly constant in cases of malignant hypertension. This finding agrees with that previously reported in autopsy cases. An attempt has been made to relate the microscopic findings in these cases with the ophthalmoscopic examination of the retinal arteries, the appearance of the nail-fold capillaries and other clinical findings.

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If such large quantities of urea can be retained in the body without affecting the non-protein nitrogen of the blood, current theories which claim that urea is equally distributed throughout the fluids of the body, are untenable. Furthermore, one should expect nitrogen thus retained to be swept out in subsequent periods if urea is, as has been generally believed, an obligatory waste end product of metabolism which must be excreted.

Other studies aimed to determine more accurately the fate of urea are being undertaken.

*An Analysis of the Adrenalin Reaction and Its Relation to the Blood Chemistry etc.* By WILLIAM F. PETERSEN, Chicago, Ill.

The effect of adrenalin on the blood pressure has been studied in 100 so called normal individuals, as well as in some 75 patients and the results of the systolic blood pressure correlated with blood chemistry (calcium, potassium, phosphate, sugar, etc.) as well as with the basal metabolism, the albumin-globulin ratio and the physical examination of the patient. In addition, the reaction of the skin to pharmacological substances has been followed in the same patients. The range of the reaction for the normal, as well as for the exaggerated reactions of the vagotonic and sympatricotonic individuals has been determined.

*Physiological Factors Influencing Inorganic Salt Secretion.* By RAY FARQUHARSON, and WILLIAM SALTER, (by invitation) and JOSEPH C. AUB, Boston, Mass.

Four patients were studied to determine the effects of exercise, change of diet and ingestion of acid and base upon their inorganic salt secretion.

We determined the calcium, phosphorus and total base of urine and feces, the ammonia, titratable acid, chlorides, sulphates and nitrogen in the urine, and the serum calcium, phosphorus, carbon dioxide and protein. The diet was then varied from a neutral to an acid diet and periods with alkalis, ammonium chloride and acid phosphates were given. The effect of rest in bed was also studied.

The results demonstrate the extent of physiological changes which may occur in the organism with respect to inorganic salt secretion. The importance of such observations as a basis for the study of abnormal conditions is obvious.

*Pleural and Pulmonary Lesions in Rheumatic Fever.* By JOHN R. PAUL, Philadelphia, Pa.

The study reported below is essentially a pathological one based upon material from a series of 28 autopsies performed upon patients who died in the active stages of rheumatic fever. The basis of selection of these cases was the

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Frank early lobular pneumonia of proven bacterial origin has been a relatively uncommon finding in our series

*A Study of Prolonged Auriculo-ventricular Conduction in Rheumatic Fever* By ROBERT L. LEVY and (by invitation) KENNETH B. TURNER, New York City, N. Y.

A comparison has been made of the incidence of prolonged A-V conduction in rheumatic fever and in other diseases. The material is taken from a general medical service during a ten year period. The following points are made: (1) prolonged A-V conduction is an important criterion in the recognition and differential diagnosis of rheumatic carditis, (2) prolonged conduction may afford evidence of the presence of myocardial lesions long after the clinical signs of rheumatic disease have subsided, (3) in four cases, prolonged conduction has been found during or shortly after an attack of acute tonsillitis, in the absence of other evidence of rheumatic infection, (4) in certain instances, there appears to be a definite relationship between variations in conduction time and salicylate medication. In these cases, salicylate apparently exerts a favorable effect upon the lesions in the heart muscle.

*Observations on Goitre in Laboratory Rabbits* By ALAN M. CHESNEY, and (by invitation) BRUCE WEBSTER and THOMAS A. CLAWSON

A high incidence of goitre has been observed in a series of 486 rabbits which were used for the study of experimental syphilis and have been under observation for varying intervals from September 1924 until the present time. The frequency and extent of the condition have been such as to warrant the use of the term "endemic goiter." The animals were fed upon a standard diet of oats, cabbage and hay, and were not given water to drink. The development of the goitre was not related to any particular breed of rabbits, but was definitely related to the time the animals had been caged. It developed in non-syphilitic as well as in syphilitic rabbits.

The enlargement of the gland was diffuse and involved isthmus as well as both lobes. The glands were vascular and histologically showed marked hyperplasia with relative scarcity of colloid. In a few, foci of lymphocytic infiltration were observed. Many of the animals died in a cachectic state, without signs of terminal infection and in these the absence of body fat was striking.

The heat production in the goitrous animals was found to be 16 per cent below that of "normal" rabbits on the average. Some animals showed a rising metabolic rate prior to death. The administration of Lugol's solution by mouth in doses of 1 minim per day was followed by a prompt rise in the metabolic rate,

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*The Relation of the Hyperglycemia to the Renal Threshold in Older Diabetics and Its Clinical Significance* By ALBERT A. EPSTEIN, New York City, N. Y.

In the resting or fasting stage of the normal individual the blood sugar level is maintained by two factors, namely, sugar mobilization and sugar utilization. After feeding, the sugar level rises and the curve which the hyperglycemia follows is small in amplitude and of short duration.

In the resting stage of the diabetic the blood sugar level depends upon three factors, namely, sugar mobilization, sugar utilization, and sugar excretion. After feeding, the level of the blood sugar rises sharply and the hyperglycemia is of long duration.

*There is a distinct difference in the curves of the blood sugar levels of early and late diabetes.* This difference is ascribed to a change in the renal threshold for sugar. The relation of the renal threshold to the blood sugar level is of two-fold character. On the one hand, interference with the excretion of sugar (renal impermeability) causes a progressive rise in the blood sugar level, on the other, readjustment of the level of carbohydrate utilization in which the kidney participates (renal tolerance) leads to an elevation of the blood sugar which remains constant and represents a condition in which a balance between the rate of sugar mobilization and sugar utilization throughout the body has been established.

The differences which early and late cases of diabetes show in their reaction to insulin with respect to the blood sugar level indicate that the persistent hyperglycemia in older or late diabetics is the result of a conservative process and represents an altered state in carbohydrate metabolism. Recognition of this fact is important in the interpretation of the blood sugar findings in the different stages of diabetes and in the application of insulin in its therapy.

*On the Significance of the Respiratory Quotient after Carbohydrate Ingestion* By WALTER R. CAMPBELL and (by invitation) S. SOSKIN, and E. J. MALTBY, Toronto, Canada.

With the respiration calorimeter of Macleod we have confirmed on dogs the differences recently reported in the "respiratory quotient" after administration of glucose and dihydroxyacetone. After administration of 25 grams glucose the respiratory quotient rises gradually to a maximum value of one, then gradually decreases, while after dihydroxyacetone it rises sharply to a maximal value often

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*Metabolic Disturbances in White Snake Root Poisoning* By H. A. BULGER and F. M. SMITH (by invitation) and D. P. BARR, St. Louis

It is now well established that the disease known as "milk sick" is caused by the injection of milk from cows feeding on white snake root (*Eupatorium urticatifolium*). Preliminary experiments on animals poisoned by this plant have indicated that such studies present a new field for the investigation of ketosis and of fat and carbohydrate metabolism. They also suggest the cause of certain clinical features of "milk sick" and indicate rational treatment of this mysterious malady. We have found that it is ordinarily impossible to produce more than a slight ketosis in rabbits. When poisoned with white snake root they developed a marked acetonemia and acetonuria. Hypoglycemia was a prominent feature of the intoxication in these rabbits, most animals died with hypoglycemic convulsions. Another prominent feature was a lipemia which may be extreme. Glucose followed by a high carbohydrate diet apparently restored the animals to health. The fatigue and rapid recurrence of symptoms following exertion in "milk sick," the coma and occasional convulsions suggest a relationship to hypoglycemia.

*The Isolation and Purification of a New Reducing Urinary Compound* By HILDING BERGLUND and (by invitation) GRACE MEDES and ANNE LOHMANN, Minneapolis, Minn.

*The Circulation in the Pneumonic Lung as Studied by Means of Temperature Measurements during Diathermy* By CARL A. L. BINGER, and (by invitation) ROYALD V. CHRISTIE, and WILHELM EHRLICH, New York City, N. Y.

Previous studies have shown us that the lung of the normal dog can be heated only slightly ( $0.4^{\circ}\text{C}$ ) above the systemic temperature. The cooling mechanism which dissipates the heat and prevents its localization in the lung was found to depend upon the pulmonary circulation rather than upon ingress and egress of air through the trachea and bronchi.

In this study an experimental pneumonia was produced in dogs by the insufflation of pneumococci and of *B. Friedlaenderi*. The temperature of the consolidated and normal lobes was measured by thermocouples while high frequency currents were passed through the dogs' thoraces. It was found that the pneumonic lobe was heated slightly ( $1^{\circ}$  to  $2^{\circ}\text{C}$ ) above the systemic temperature and the temperature of the normal lobes. The change was of the same order of magnitude as seen in lungs with obstructed pulmonary arteries.

The experimental data were correlated with the gross and histologic appearance of the lungs, which furnished an explanation for the heat retention on the basis of an impaired circulation. This appeared to be due to the pressure of the intra-alveolar exudate which resulted in an ischemic state in which the alveolar capillaries were empty of blood. The impairment of the circulation was further substantiated by post-mortem barium-gelatin injection preparations, which showed

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With the exception of three patients, the velocity of the pulmonary and of the venous blood flow after strophanthin or digitalis was either unchanged or increased in all the patients with cardiovascular disease. Although the average cardiac rate showed a reduction (10 per cent) the average velocity of pulmonary blood flow increased 35 per cent and that of the peripheral venous blood flow by 25 per cent. In all the patients in whom digitalis caused a definite improvement in the clinical behavior, the velocity of blood flow was definitely increased. The other three patients showed a slowing (20 per cent) of the pulmonary flow, with no change in the velocity of the venous blood flow. Proportionate to the slowing of the pulmonary blood flow there was a reduction in the pulse rate.

The observations by others that digitalis decreases the minute volume output, and the finding that it has no effect or that it increases the velocity of blood flow can be reconciled only if digitalis decreases the cross sectional area of the vascular bed, under which condition unchanged velocity would inevitably yield a decreased minute volume. Blood volume studies in addition to the measurements of the velocity of blood flow were performed on several patients in order to clarify this problem.

*The Initial Effect of Moderate Undernutrition upon the Weight Curve in the Obese*  
By MARK FALCON-LESSES, (by invitation) and L. H. NEWBURGH, Ann Arbor, Mich.

The initial effect, upon the weight curve in the obese, of the shift from a maintenance diet to one of moderate undernutrition is the production of a tri-phasic curve. The three phases occur as follows: (1) The first phase is one of excessive weight loss lasting from two to seven days. (2) The second phase is one of weight maintenance and failure to lose weight, despite the sub-maintenance calories—lasting five to fifteen days. (3) The third phase is one of excessive weight loss lasting two or three days. This tri-phasic curve does not occur if the caloric value of the diet is excessively sub-maintenance but it has been produced in every obese person so far studied.

The first phase seems intimately connected with the katabolism of glycogen, since it occurred when the subjects were in nitrogen balance and the weight losses were much too great to be accounted for by the katabolism of fat.

The second phase is one of hydration due to the retention of water as shown in water-balance studies.

The third phase is one of dehydration, apparently due to the loss of the excess water stored up during the weight-holding period. At the end of the third phase, the weight is exactly where it should be as calculated from the theoretical weight loss.

*The Role of Carbohydrate in Obesity With Special Reference to the Treatment of Obesity Complicated by Hypertension and Cardiac Disorders* By BURGESS GORDON, and (by invitation) C. W. NISSLER, Philadelphia, Pa.

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*Experimental Leukocytosis and Leukopenia* By PAUL REZNIKOFF, New York City, N Y

Recent investigations of Minot, Murphy and Cohn indicate that erythrocytic stimulation by chemical means is possible Doan and his coworkers have presented evidence that myelocytic stimulation may also be induced by nucleoproteins and nucleotides They obtained a preliminary leukopenia with nucleoprotein which they ascribed to the activity of the spleen but with nucleotides an immediate leukocytosis occurred

In the experiments reported here, nucleoprotein from liver and thymus (Dr John A Mandel), nucleic acid from yeast and thymus (Dr Marvin V Buell, Dr P A Levene), and adenine sulphate and guanine hydrochloride (Mr Kenneth Blanchard, Dr Henry Jackson, Jr) were injected intravenously into rabbits When solutions of these substances in phosphate buffers were introduced, a leukopenia occurred, at first of the myelocytic forms and then, of the lymphocytes The myelocytic leukopenia was of short duration and was succeeded by a marked and sustained polynucleosis Increases in total cell count from 20,000 to 79,000 have been obtained with no apparent ill effects Solutions of phosphates caused a marked lymphocytic leukopenia This did not occur with NaCl or aqueous solutions containing no inorganic phosphate During the state of polynucleosis a marked shift to the left took place, indicating increased young cell formation or marked chemotaxis

*The Development of the Ethyl Iodide Method for Determining the Cardiac Output of Man, a Test of the Method by Estimations of Flow through Dogs' Lungs Perfused at a Known Rate* By ISAAC STARR, JR, and (by invitation) CLARENCE JAMES GAMBLE Philadelphia, Pa

In anesthetized dogs, the ethyl iodide content in mixed venous blood does not change materially during rebreathing The ethyl iodide content estimated from rebreathed air and the coefficient of distribution agrees with that found by analysis of mixed venous blood taken before rebreathing started The content in arterial blood agrees with the value calculated from alveolar air This permitted the measurement of flow by ethyl iodide while perfusing dogs' lungs at a known rate, satisfactory agreement resulting in five of six experiments

In normal persons breathing ethyl iodide the arterial content (by analysis) is correctly estimated from alveolar air collected automatically The ethyl iodide content in rebreathed air remains constant or falls very slowly during rebreathing for 12 minutes, therefore we believe the content in mixed venous blood can be estimated as in dogs

The technique for the determination of blood flow in man is that of Henderson and Haggard, followed by rebreathing for thirty seconds, and determining the subject's distribution coefficient, (average normal blood = 6.1) Consecutive estimations on subject G reclining on three days = 3.9, 4.1, 4.0, 4.1, 4.0, 3.9, 3.9 On S (on three days) 5.3, 4.9, 4.1, 3.4, 4.6, 3.3, 3.0, 2.9, 3.5 liters per minute

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of fluids, accurate measurements of the vessels by micrometry and photography have been made. It has been determined that the cerebral vessels may show changes in diameter consistent with mere passive expansion or collapse, following abrupt rise or fall in arterial pressure. In addition, the arteries show changes exactly opposite in direction to these passive changes. These can be brought about by stimulation of constrictor or dilator nerves, and by alteration of the chemical and physical (osmotic tension) constitution of the blood.

It was concluded that the cerebral circulation is not altogether *passively* regulated, i.e., from a distance by splanchnic or general systemic vasoconstriction and dilatation. It is also dependent upon an active vasomotor mechanism for cerebral vessels, and by changes in the physical and chemical characteristics of the blood.

In addition to vasomotor, osmotic tension and drug actions, other dilator mechanisms have been studied. It has been determined that cerebral artery vasodilatation follows (1) reduction in the quantity of arterial blood circulating through the brain (severe hemorrhage, clamping the carotid arteries, circulatory failure and increased intracranial pressure), (2) reduction in the oxygen content of the arterial blood circulating through the brain (carbon monoxide), (3) increase in carbon dioxide content of the arterial blood circulating through the brain, (4) intravenous injection of acid or acid producing substances (lactic acid, acetone).

Hypothetically, these experimental changes in the quantity and quality of the blood create a physiological emergency. They were always associated with cerebral vasodilatation.

*The Adaptation of the Circulation to Hyperthyroidism and to Hypothyroidism.* By HERMANN L. BLUMGART and (by invitation) SAMUEL L. GARGLE, Boston, Mass.

The purpose of the investigation was to learn in what manner and to what degree the circulation of blood is accelerated to enable the transport of larger quantities of oxygen to the over-active tissues of thyrotoxic patients. Ten thyrotoxic patients of different types have been studied. The basal metabolic rates range from plus 11 to plus 50 per cent. The speed of blood flow through the lungs was considerably faster than the average normal (10.8 seconds) in every patient studied. In some patients the velocity of blood flow was more than twice the normal. The velocity of venous blood flow from the arm to the heart was likewise greatly increased. The extent of increase of the velocity of blood flow and of the basal metabolic rate were in general, proportional. The vital capacity was reduced in all subjects even in the absence of any signs of congestive failure—an observation in accord with other studies. The conspicuous strain under which the heart labors even under basal conditions in maintaining such an increased velocity of blood flow is undoubtedly an important factor in causing frequent occurrence of heart failure in thyrotoxic states.

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*Effect of Some of the Purin-base Diuretics upon the Coronary Flo.* By N C GILBERT and (by invitation) G K FENY, Chicago, Ill

Previous experimental work has shown the purin-base diuretics to have a vasodilator effect upon the coronary arteries, and to increase the coronary flow. This has not been completely confirmed by all investigators, and the objection has been made that the doses used were larger than the human therapeutic doses.

Because of the beneficial therapeutic results, further experimental work was done upon the intact animal. Under different methods of anesthesia a modified Morovitz cannula was inserted into the coronary sinus and the volume flow measured by means of a piston recorder tracing on a revolving drum. The doses used were low average human equivalents, and fractions of these: Theobromine sodium salicylate and acetate 0.01 gm per kilogram, theocine sodium acetate 0.0032 gm per kilogram, caffeine sodium benzoate 0.0066 gm per kilogram and ephyllin 0.0014 gm per kilogram. A definitely increased coronary flow was obtained with each of these, in the presence of a decreased systolic and diastolic pressure. Except when an extreme vasodilatation was already present, the increased coronary flow was apparently constant, with these drugs. In the case of the theobromine salts, the increased flow resulted in some cases with one-eighth of the above doses. In the case of ephyllin, theocine, and caffeine, results with less than one-half of the above doses were uncertain. The effect of anesthetics used on coronary flow was considered. Chloretone was shown to have an extreme vasodilator action.

*Studies on Experimental Auricular Fibrillation Produced by Multiple Stimuli*  
By ARTHUR D HIRSCHFELDER Minneapolis, Minn

Auricular fibrillation can be produced in the exposed heart of the dog by stimulating either auricle with a single make and break shock thrown in rapid succession into three neighboring parts of the auricular wall. This is accomplished by means of three separate currents sent in rapid succession through four electrodes composed of blunt pointed copper wires about three millimeters apart, applied to the wall of the auricle.

The primary circuits to the three induction coils are made and broken by passing the current through a rapidly revolving drum covered with a perforated paper. As each perforation passes a spring wire which completes the circuit, the current is made and broken. Three perforations are located in an oblique row to insure sequence. A single cycle of three separate stimulations sets up circus movements which invariably produce auricular fibrillation. Fibrillation produced in this way often lasts much longer than that produced by ordinary faradization and frequently lasts from ten minutes to more than half an hour. Duration seems independent of cardiac weakness. Lasting fibrillation seemed to occur most commonly in slow hearts and in pilocarpinized animals. Stimuli to the auricle applied during sympathetic stimulation or after adrenalin following atropin, gave rise to fibrillation lasting only a few seconds. Further experiments are in progress.

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*Whole Blood Immunity in Lobar Pneumonia* By R. L. CECIL, and (by invitation) D. R. RHOADES, and W. D. SUTLIFF, Washington, D. C.

The pneumococidal power of whole, uncoagulated blood has been measured. The method in brief consists in determining the number of pneumococci which 0.5 cc. of human blood will kill in 24 hours. Heparin is the anticoagulant used.

The number of pneumococci killed varied as follows:

(a) In ward patients with minor complaints and without a history of lobar pneumonia: from none to 10,000.

(b) In patients convalescing from lobar pneumonia: from 100,000 to 10,000,000.

The following changes were observed in lobar pneumonia:

1. In the acute stage pneumococidal power is normal or less than normal.

2. When bacteremia is present before the crisis, no pneumococidal power is present.

3. Shortly before or at the time of crisis the pneumococidal power of the whole blood becomes greater than normal.

4. The pneumococidal power of the whole blood reaches its highest point after the crisis.

5. The simultaneous occurrence of bacteremia (250 colonies of pneumococcus Type I per cubic centimeter of blood) and pneumococidal power of high degree was encountered in a patient who developed acute pneumococcal endocarditis following Type I lobar pneumonia.

6. Felton's antipneumococcus serum was administered to pneumonia patients with normal or subnormal pneumococidal power. Tests of these patients' blood made 24 hours after the injection of serum usually showed whole blood immunity fully as great as that found after spontaneous recovery from the disease.

*The Skin Temperature in Diabetes* By HOWARD F. ROOT, Boston, Mass.

The temperature of the skin of 19 diabetics was determined by a method consisting of two copper-constantan junctions, one located in a constant temperature bath—a Devair flask—and the other applied to the skin. The resulting current, which is measured on a galvanometer, is proportional to the difference in temperature between the two junctions.

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previously reported studies of the effect of changes in acid-base relationships on epileptic seizures, permit a clearer analysis than has yet been possible of the physiological processes in the brain which contribute to seizures

*Toxemia of Intestinal Obstruction, and Ileus Clinical Deductions Regarding its Nature and Treatment* By CHARLES S McVICAR and (by invitation) JAMES T WEIR, Rochester, Minn

Inhibition of gastro-intestinal motility, whether due to organic or functional causes, is attended with grave consequences. Death ensues if an organic obstruction persists and is equally a danger if functional inhibition is not relieved. Animal experimentation has advanced knowledge with regard to this, and is directly responsible for the discovery that the toxic condition preceding death is associated with characteristic disturbances in the chemistry of the blood, namely nitrogen retention, alkalosis and hypochloremia. Estimations of the chemical changes in the blood enable one to measure the severity of the toxemia and to estimate progress in treatment. Animal experiments have as a rule been directed to the determination of the cause of death and while this is eminently desirable it is equally important that studies be made of earlier clinical manifestations and morbidity.

It was observed that the toxic manifestations of motor inhibition were associated with diminished urinary output, and routine treatment now consists in maintaining adequate fluid intake to compensate for the loss of fluids by vomiting or by lavage of gastric contents. It has been found that the intravenous route of administration is most satisfactory, since the oral route is precluded by vomiting, clysmata are soon rejected or lost because of incontinence, and subcutaneous administration is exceedingly uncomfortable if sufficient amounts are given. For intravenous injection a solution is used containing 10 grams of sodium chloride and 100 grams of glucose to a liter of freshly distilled sterile water. It was found that the intravenous administration of sodium chloride solution was not invariably followed by diuresis, and the glucose was added to insure urinary excretion.

As clinical experience enlarged it became evident that cases could be grouped arbitrarily into (1) fatal cases with marked disturbances in the chemistry of the blood and anuria, at necropsy renal injury may be demonstrated, (2) severe toxemia also associated with marked changes in the chemistry of the blood and oliguria which, however, respond to intensive treatment and the patients recover without any discoverable evidence of renal injury, (3) mild toxemia with diminished urinary output and characteristic but moderate changes in the chemistry of the blood, the patients respond quickly to treatment, (4) clinical manifestations of motor inhibition, namely, vomiting and gastric retention with a low output of urine but without disturbance in the chemistry of the blood. The last group is of special interest because if the earliest clinical manifestations of ileus may be recognized before changes occur it follows that the toxic syndrome is not due to a disturbance in the chemistry of the blood. It was found, moreover, that in the

previously reported studies of the effect of changes in acid-base relationships on epileptic seizures, permit a clearer analysis than has yet been possible of the physiological processes in the brain which contribute to seizures

*Toxemia of Intestinal Obstruction, and Ileus Clinical Deductions Regarding its Nature and Treatment* By CHARLES S McVICAR and (by invitation) JAMES F WEIR, Rochester, Minn

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This degree of new glucose formation has been observed in two patients. The diet in each case was high in fat and low in protein and carbohydrate. In one case, a diabetic of moderate severity, the process was stimulated by thyroid extract, and over a period of ten days the glucose excreted in the urine exceeded G by 128 grams. In the other case, one of diabetes of unusual severity, insulin could be discontinued for only twenty-four hours while the patient was receiving such a diet. During this period of twenty-four hours the glucose excretion exceeded G by amounts as great as 100 grams on two occasions. Respiratory quotients were observed as low as 0.67.

In both patients the observations were terminated by the development of extreme ketosis and acidosis, the carbon dioxide combining power falling to 19 or 20 volumes per cent. The development of severe ketosis under these conditions suggests that these figures represent the maximum power of new glucose formation in diabetes mellitus.

*Hypoglycemic Reactions in a Diabetic without Insulin* By HOWARD F. WEST and BERTVARD SMITH, Los Angeles, Calif.

This report concerns observations on the case of a boy who developed diabetes at the age of fourteen with coma. He was seen first by the authors when in deep coma in April, 1924, one year after onset of diabetes. The second period of coma was the result of discontinuing insulin and routine diet. For the subsequent two years he ran a typical diabetic course, requiring from forty to fifty units of insulin per day while on a diet allowing 90 grams of carbohydrate per day with some variations in fat from time to time to avoid overweight. In October, 1926, following acute ketosis (pre-coma) due to irregularities in diet and insulin, he developed sensitiveness to insulin which was discontinued. For the following two months he was subject to severe and typical hypoglycemic shocks though the carbohydrate value of his diet was increased to 170 grams per day with supplementary feedings of carbohydrate food at times of severe reactions. During this period his blood sugar varied from 19 mgm. per hundred to 668 mgm. in an entirely erratic and unpredictable manner.

After a period of about three months he became stabilized and remained in good condition on a diet allowing 170 grams of carbohydrate without insulin. In November, 1927, following an acute respiratory infection he again developed acute ketosis and glycosuria. Insulin was again required for control. After three weeks of treatment he again developed sensitiveness to insulin and for several weeks after insulin was discontinued he was subject to frequent hypoglycemic reactions with occasional periods of unconsciousness and convulsions in spite of high carbohydrate intake with frequent feedings. He again became stabilized and is now in apparent good health and free from glycosuria on a diet allowing 180 grams of carbohydrate per day without insulin.

The only significant physical findings during the hypoglycemic periods were an enlarged and tender liver, moderate edema and, on occasion, traces of bile in the urine.

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The initial data show an average weight of 222 pounds, 72 per cent above normal, and average surface 2.0 square meters, 26 per cent above normal. The calories-per-hour average 71, giving an average basal metabolic rate of -2.0 per cent as usually calculated, but actually 23 per cent above the calories produced at normal weight. Conversely, it may be stated that the increase in basal calories corresponds to the increase in surface (26 per cent) but not to that of weight (72 per cent). There is no evidence of a metabolic economy in obesity but rather an excessive energy exchange.

After reduction, the average losses were 41 pounds and 0.17 square meters corresponding to a diminution of 47 per cent of the excess weight and 45 per cent of the excess surface. The calories-per-hour average 61, a drop of 10 calories or 77 per cent of the excess energy. Hence there is a definite decrease in energy exchange coincident with weight reduction. The rate of change of calories is, however, over  $1\frac{1}{2}$  times as great as the rates of change of either weight or surface. This evidence indicates again that body surface is not the sole regulator of metabolism.

*Observations on the Circulation of Guinea Pigs during Bronchospasm.* By F. M. SMITH and J. S. HARTER (by invitation) and H. L. ALEXANDER, St. Louis, Mo.

In order to determine the extent of filling of the heart during bronchospasm, the effective right auricular pressure was calculated.

*Method.* Large guinea pigs (650 to 1000 grams) were sensitized by intraperitoneal injections of egg white. Under amylal anesthesia, cannulae were placed in the left carotid artery, in the right auricle (through the external jugular vein) and in the right pleural cavity. Simultaneous pressures were recorded by tracings as were respiratory volumes. Bronchospasm was then induced by intravenous injection of egg white and the circulatory response in relation to intrapleural pressure and depth of respiration noted.

*Results.* Unless bronchospasm comes on very suddenly there is a decreased filling of the right heart until asphyxia supervenes. This is determined by plotting the algebraic difference between the mean right auricular pressure and the mean intrapleural pressure. This gives the effective right auricular pressure which indicates degree of filling. Sudden bronchospasm induces normal or increased filling.

*Serum Electrolytes in Infections and Nephritis.* By J. H. AUSTIN, and (by invitation) F. WILLIAM SUNDERMAN and J. G. CAMACK.

The serum electrolytes in infections and nephritis were studied in the same manner as previously reported in lobar pneumonia. In lobar pneumonia, tuberculosis, chronic glomerular nephritis, and mercurial poisoning there was found a

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In one case of "complete" myxedema there was no reaction after the ingestion of iodine. This was to be expected from the previous experiments on dogs, in which a removal of the thyroid caused a disappearance of the urinary reaction to iodides. There was a similar lack of response in a case of Addison's disease, but the results in this case are more doubtful, as the patient died a short time after the experiment.

Of course, the chief interest in this connection is the study of nephritis. So far, we have been able to study only two types, one, the hemorrhagic subacute type, in which there was a prolonged delay in the excretion of nitrogen after iodides, but in which the increased excretion of nitrogen after salicylates occurred promptly. On the contrary, in a case which partakes somewhat of the character of nephrosis, there is a tendency to a reversal of this mechanism.

The significance of these observations is not clear at present, but the indication seems to be that there is some fundamental disturbance in the nitrogen metabolism, not dependent upon the insufficiency of the kidney as a filter.

*Blood Volume Preceding and Following Splenectomy* By H. Z. GIFFIN, GEORGE E. BROWN, with technical assistance of GRACE M. ROTH

This study was undertaken because of the fact that no data have been published on the spleen and splenectomy with relation to blood volume in man. Observations were made on six cases of primary splenomegaly without anemia, eleven cases of hemolytic icterus, and eighteen cases of splenic anemia. The Congo-red method was used to determine the blood and plasma volume.

In fifty normal individuals, Brown, Rowntree and Roth, the mean values were as follows: total blood volume 89 cc per kilogram, plasma volume 50 cc per kilogram, cell volume 39 cc per kilogram, and circulating hemoglobin 15 grams per kilogram.

Primary splenomegaly without anemia showed a mean blood volume of 102 cc per kilogram, plasma volume 60 cc per kilogram, and a cell volume of 42 cc per kilogram,—a simply hypervolemia, suggesting the possibility that in primary splenomegaly without anemia the enlarged circulatory bed due to the splenomegaly and enlarged blood vessels necessitates a larger blood volume for circulatory needs.

Hemolytic icterus before splenectomy showed a blood volume of 93 cc per kilogram, plasma volume of 74 cc per kilogram, and a cell volume of 19 cc per kilogram,—an oligocythemic normovolemia. After splenectomy in hemolytic

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*The Importance of Hematological Evidence in the Diagnosis of Pernicious Anemia*

By C. P. HOWARD, and (by invitation) E. S. MILLS, Montreal, Canada

The authors have studied a series of 28 cases diagnosed as pernicious anemia at the Montreal General Hospital. Only cases which were thoroughly investigated and subsequently followed, were accepted. The object of the study was to test the reliability of hematological evidence.

Twenty-three cases had a blood picture characteristic of the disease, while the remaining five were atypical in this respect, though classical in other ways. When the latter group was subsequently followed the diagnosis in each instance was called into question. Not one of these responded to liver treatment.

A high color index, a large type of red cell, and a leucopenia with relative lymphocytosis, are constantly present in pernicious anemia. In our experience cases which fail to show this blood picture are subsequently shown to be incorrectly diagnosed.

There is a type of anemia occurring in young women which often begins during pregnancy and is refractory to ordinary treatment, which clinically resembles very closely true pernicious anemia, but has a distinct blood picture.

*Blood Groups among Maya Indians of Yucatan* By W. L. MOSS and (by invitation) JAMES A. KENNEDY, Boston, Mass., and Rochester, New York

During the last decade considerable interest has been manifest in determining the percentage distribution among the four blood groups of the population in the various countries of the world.

Geneticists have been active in collecting this data and have attempted to apply it to the investigations of racial origins and relationships.

The bloods herein reported were collected during the summer of 1927 by Dr. G. E. Williams, a member of the Carnegie Expedition to Yucatan.

Blood for serum was collected in Wright's tubes and after coagulation, the serum was taken up in capillary tubes, the ends of which were sealed in the flame. Blood for corpuscles was taken in a preserving fluid recommended by Rous and Turner (J. Exper. Med., 1916, xxiii, 219), consisting of a mixture of two parts of isotonic sodium citrate solution and five parts isotonic dextrose solution. This mixture was put up in U-shaped tubes and after the introduction of one or two drops of blood the ends were sealed in the flame.

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TABLE 1

## Individual case analyses

| Case number                           | Diagnosis  | Date (1927)                            | Temperature<br>°F.     | Pulse<br>per<br>min<br>site | Respiration<br>per<br>min-<br>ute | Total base                 |                                  |                      | Cl<br>m Eq<br>per<br>liter | CO <sub>2</sub><br>mM<br>per<br>liter | Protein<br>grams<br>per<br>100 cc | Specific gravity<br>20 C.<br>20 C. | Non protein nitrogen<br>mgms<br>per<br>100 cc | Calculated  |  |   |          |
|---------------------------------------|--|--|------------------------|-----------------------------|-----------------------------------|----------------------------|----------------------------------|----------------------|----------------------------|---------------------------------------|-----------------------------------|------------------------------------|---|---|--|---|----------|
|                                       |  |  |                        |                             |                                   | Chemically deter-<br>mined | 1/17 X corrected<br>conductivity | Average              |                            |                                       |                                   |                                    |   | HCO <sub>3</sub> <sup>-</sup><br>m Eq<br>per<br>liter | B Pr (2.03 Pr)<br>m Eq<br>per<br>liter | Residual anions<br>m Eq<br>per<br>liter |          |
| Normal values {<br>Minimum<br>Maximum |  |  |                        |                             |                                   | m Eq<br>per<br>liter       | m Eq<br>per<br>liter             | m Eq<br>per<br>liter |                            |                                       |                                   |                                    |   |   |  |   |          |
|                                       | A 10   | Tuberculous<br>meningitis              | March 15               | 100 2                       | 98                                | 30                         | 144                              | 146                  | 145                        | 92                                    | 25 1                              | 8 6                                | 1 0281  | 33 3  | 24                                     | 17                                      | 12       |
|                                       | A 11   | Pleural effusion                       | March 17               | 99 4                        | 136                               | 24                         | 147                              | 145                  | 146                        | 100                                   | 24 5                              | 5 1                                | 1 0187  | 32 3  | 23                                     | 10                                      | 13       |
|                                       | A 12   | Generalized<br>tuberculosis            | March 25<br>March 31   | 100 4<br>99 6               | 116<br>124                        | 34<br>38                   | 154<br>142                       | 144<br>148           | 149<br>145                 | 90<br>89                              | 25 3<br>26 5                      | 9 5<br>9 5                         | 1 0315<br>1 0317                              | 29 7<br>53 7  | 24<br>25                               | 19<br>12                                | 16<br>12 |
| A 13                                  | Acute proliferative<br>pulmonary<br>tuberculosis | February 15<br>February 22             | 102 0<br>100 0         | 108<br>112                  | 32<br>28                          | 160<br>159                 | 149<br>156                       | 155<br>158           | 97<br>96                   | 24 8<br>28 0                          | 8 7<br>9 3                        | 1 0320<br>1 0313                   | 37 7  | 24<br>27  | 18<br>19                               | 16<br>16                                |          |
| A 14                                  | Miliary tuberculosis                             | April 26                               | 102 8*                 | 112                         | 40                                | 138                        | 148                              | 143                  | 87                         | 27 5                                  | 7 5                               | 1 0256                             |   | 26  | 15                                     | 15                                      |          |
| A 15                                  | Pleural effusion,<br>pulmonary<br>tuberculosis   | February 22<br>March 3<br>February 22† | 102 0<br>101 4<br>99 0 | 132<br>116<br>80            | 32<br>29<br>26                    | 149<br>147<br>147          | 139<br>142<br>136                | 144<br>142<br>150    | 98<br>85<br>94             | 23 6<br>26 8<br>27 4                  | 7 7<br>8 7<br>7 8                 | 1 0280<br><br>1 0250               | 27 1  | 22<br>26<br>26  | 16<br>18<br>20                         | 8<br>13<br>14                           |          |
| A 16                                  | Pleural effusion                                 | March 31<br>March 31†                  | 99 0<br>98 2           | 80<br>102                   | 24                                | 147<br>146                 | 153<br>145                       | 150<br>146           | 94<br>94                   | 27 4<br>10 7                          | 7 8<br>5 9                        | 1 0266<br>1 0229                   | 23 2<br>41 9                                  | 26<br>9   | 16<br>12                               | 14<br>31                                |          |
| A 17                                  | Acute nephritis                                  | March 7                                | 98 2                   | 102                         | 24                                | 156                        | 157                              | 157                  | 96                         | 25 5                                  | 7 2                               | 1 0257                             | 49 3  | 24  | 15                                     | 22                                      |          |
| A 18                                  | Eclampsia  | February 16                            | 101 0                  | 140                         | 20                                | 153                        | 143                              | 148                  | 97                         | 15 6                                  | 6 8                               | 1 0254                             | 46 5  | 14  | 14                                     | 23                                      |          |
| A 19                                  | Bichloride of mercury<br>poisoning               | June 10                                | 98 2                   | 72                          | 22                                | 147                        | 166                              | 166                  | 76                         | 23 5                                  | 9 0                               |                                    | 282 0   | 22  | 18                                     | 41                                      |          |

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|                                    |  |              |                   |                            |                                   | Chemically deter-<br>mined | 1.17 X corrected<br>conductivity | Average | HCO <sub>3</sub> <sup>-</sup><br>mEq<br>per<br>liter |                           |                                       |                                   |                                  |  | B Pr (2.03 Pr)<br>mEq<br>per<br>liter | Residual anions<br>mEq<br>per<br>liter |  |  |
| Normal values { Minimum<br>Maximum |  |              |                   |                            |                                   |                            |                                  |         |  |                           |                                       |                                   |                                  |  |                                       |  |  |  |
| A 10                               | Tuberculous<br>meningitis                        | March 15     | 100 2             | 98                         | 30                                | 144                        | 146                              | 145     | 92   | 25 1                      | 8 6                                   | 1 0281                            | 33 3                             | 24   | 17                                    | 12                                     |  |  |
| A 11                               | Pleural effusion                                 | March 17     | 99 4              | 136                        | 24                                | 147                        | 145                              | 146     | 100  | 24 5                      | 5 1                                   | 1 0187                            | 32 3                             | 23   | 10                                    | 13                                     |  |  |
| A 12                               | Generalized<br>tuberculosis                      | March 25     | 100 4             | 116                        | 34                                | 154                        | 144                              | 149     | 90   | 25 3                      | 9 5                                   | 1 0315                            | 29 7                             | 24   | 19                                    | 16                                     |  |  |
| A 13                               | Acute proliferative<br>pulmonary<br>tuberculosis | March 31     | 99 6              | 124                        | 38                                | 142                        | 148                              | 145     | 89   | 26 5                      | 9 5                                   | 1 0317                            | 53 7                             | 25   | 19                                    | 12                                     |  |  |
|                                    |  | February 15  | 102 0             | 108                        | 32                                | 160                        | 149                              | 155     | 97   | 24 8                      | 8 7                                   | 1 0320                            | 37 7                             | 24   | 18                                    | 16                                     |  |  |
|                                    |  | February 22  | 100 0             | 112                        | 28                                | 159                        | 156                              | 158     | 96   | 28 0                      | 9 3                                   | 1 0313                            |                                  | 27   | 19                                    | 16                                     |  |  |
| A 14                               | Miliary tuberculosis                             | April 26     | 102 8*            | 112                        | 40                                | 138                        | 148                              | 143     | 87   | 27 5                      | 7 5                                   | 1 0256                            |                                  | 26   | 15                                    | 15                                     |  |  |
| A 15                               | Pleural effusion,<br>pulmonary<br>tuberculosis   | February 22  | 102 0             | 132                        | 32                                | 149                        | 139                              | 144     | 98   | 23 6                      | 7 7                                   | 1 0280                            |                                  | 22   | 16                                    | 8                                      |  |  |
|                                    |  | March 3      | 101 4             | 116                        | 29                                |                            | 142                              |         | 85   | 26 8                      | 8 7                                   |                                   | 32 2                             | 26   | 18                                    | 13                                     |  |  |
|                                    |  | February 22† |                   |                            |                                   | 147                        | 136                              | 142     | 90   | 21 1                      | 6 7                                   | 1 0250                            | 27 1                             | 20   | 14                                    | 18                                     |  |  |
| A 16                               | Pleural effusion                                 | March 31     | 99 0              | 80                         | 26                                | 147                        | 153                              | 150     | 94   | 27 4                      | 7 8                                   | 1 0266                            | 23 2                             | 26   | 16                                    | 14                                     |  |  |
|                                    |  | March 31†    |                   |                            |                                   | 146                        | 145                              | 146     | 94   | 10 7                      | 5 9                                   | 1 0229                            | 41 9                             | 9  | 12                                    | 31                                     |  |  |
| A 17                               | Acute nephritis                                  | March 7      | 98 2              | 102                        | 24                                | 156                        | 157                              | 157     | 96   | 25 5                      | 7 2                                   | 1 0257                            | 49 3                             | 24   | 15                                    | 22                                     |  |  |
| A 18                               | Eclampsia  | February 16  | 101 0             | 140                        | 20                                | 153                        | 143                              | 148     | 97   | 15 6                      | 6 8                                   | 1 0254                            | 46 5                             | 14   | 14                                    | 23                                     |  |  |
| A 19                               | Bichloride of mercury<br>poisoning               | June 10      | 98 2              | 42                         | 22                                | 147                        | 166                              |         | 76   | 23 5                      | 9 0                                   |                                   | 282 0                            | 22   | 18                                    | 41                                     |  |  |

## MATERIAL AND METHODS

Thirty-three specimens of blood serum and two pleural fluids from twenty-nine patients on the Medical Services at the Pennsylvania Hospital and at the Hospital of the University of Pennsylvania in Philadelphia were examined

The technical methods used were those employed in our previous study (1926) Chemical determinations of total base by the method of Stadie and Ross have been compared further with conductivity determined with the Christiansen ionometer corrected by the formula of Gram and Cullen We find on further study the corrected conductivity times 1.17 equals in the average the total base chemically determined and we use this factor at present instead of 1.13 reported in our previous study

An approximate figure for the base bound by protein  $[B \text{ Pr}]$  has been calculated by equation 54 of Hastings, Salvesen, Sendroy and Van Slyke (1927)

$$[B \text{ Pr}] = 0.97 [\text{Pr}] (\text{pH} - 5.26)$$

taking for pH, 7.35 Hence

$$\begin{aligned} [B \text{ Pr}]_{\text{mEq}} &\text{ is approximately } 2.0 [\text{Pr}]_{\text{gms}/100 \text{ cc}} \\ [\text{HCO}_3]_{\text{mEq}} &\text{ is taken as equal to } [\text{CO}_2]_{\text{mM}} - 1.3 \\ \text{Residual anion} &= [B] - ([\text{Cl}^-] + [\text{HCO}_3] + [B \text{ Pr}]) \end{aligned}$$

Protein was determined with the Abbe refractometer as in our previous study (1926) Specific gravity was determined at 20°C in a 2 cc pyknometer In graph 1 we have plotted all measurements of protein against specific gravity The correlation is fair

## RESULTS

Brief descriptions of each case studied are appended at the close of the paper The individual analyses are tabulated in table 1 Values outside of the normal range are in bold-faced type Groups of cases representing lobar pneumonia, tuberculosis and rheumatic fever are tabulated in table 2 showing the maximum, minimum and number of observations outside the normal range for each electrolyte in each group

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*Renal*

(Table 1, cases A 17 to A 22) The electrolyte distribution in two cases of acute nephritis (A 17 and A 21) differed from that in the pneumonia group in the fact that the reduction in chloride was compensated by an increase of one or more of the residual anions without any appreciable change in the total base. This is similar to Atchley's observations with ligation of dogs' ureters. On the other hand in our case of mercurial poisoning (A 19) with anuria for six days, two-thirds of the decrease in chloride and bicarbonate concen-

TABLE 3  
*Analyses of serum from mercurial poisoning case A 19*

|   | Case A 19             | Average normal        | Difference            |
|---|-----------------------|-----------------------|-----------------------|
|   | <i>m Eq per liter</i> | <i>m Eq per liter</i> | <i>m Eq per liter</i> |
| Total base (chemically determined)                                    | 146.5                 | 154.7                 | -8.2                  |
| BCl   | 76.2                  | 104.0                 | -27.8                 |
| BHCO <sub>3</sub> *   | 22.2                  | 25.8                  | -3.6                  |
| [B <sub>2</sub> HPO <sub>4</sub> + BH <sub>2</sub> PO <sub>4</sub> ]† | 9.4                   | 3.0                   | +6.4                  |
| B <sub>2</sub> SO <sub>4</sub>  | 12.0                  | 1.0                   | +11.0                 |
| B Pr‡   | 18.0                  | 16.0                  | +2.0                  |
| B organic acids§  | 8.4                   | 4.9                   | +3.5                  |
| pH  | 7.31                  |                       |                       |
| Non-protein nitrogen mgm per 100 cc                                   | 282.0                 |                       |                       |
| Degrees depression in freezing point                                  | 0.63°C                |                       |                       |

\* [BHCO<sub>3</sub>] = [CO<sub>2</sub>] - 1.27

†  $\frac{B_2HPO_4}{BH_2PO_4}$  at pH 7.31 =  $\frac{77}{23}$  [PO<sub>4</sub>] = 5.3 mM/L, [B<sub>2</sub>HPO<sub>4</sub> + BH<sub>2</sub>PO<sub>4</sub>] = 9.4 m Eq

‡ B Pr = 0.97 (Pr) (pH - 5.26) (Pr) = grams protein per 100 cc.

§ Calculated by difference

tration in the blood serum was accounted for as is shown in table 3 by increase in serum phosphate, sulphate and organic acid and one-third by decrease in the total base chemically determined.<sup>2</sup> There occurred in this serum a marked discrepancy between total base chemically determined and the serum conductivity so that it would not be permissible to average the value by the two methods. The cause for the discrepancy is not clear. The relative rise in phosphate, sulphate and organic acid in the serum in this case with displacement

<sup>2</sup> This case has been presented from a somewhat different aspect by J. M. Hayman, Jr and J. T. Priestley, *Am J Med Sci*, 1928 (in press). The Importance of a Diuresis in the Treatment of Certain Cases of Mercuric Chloride Poisoning

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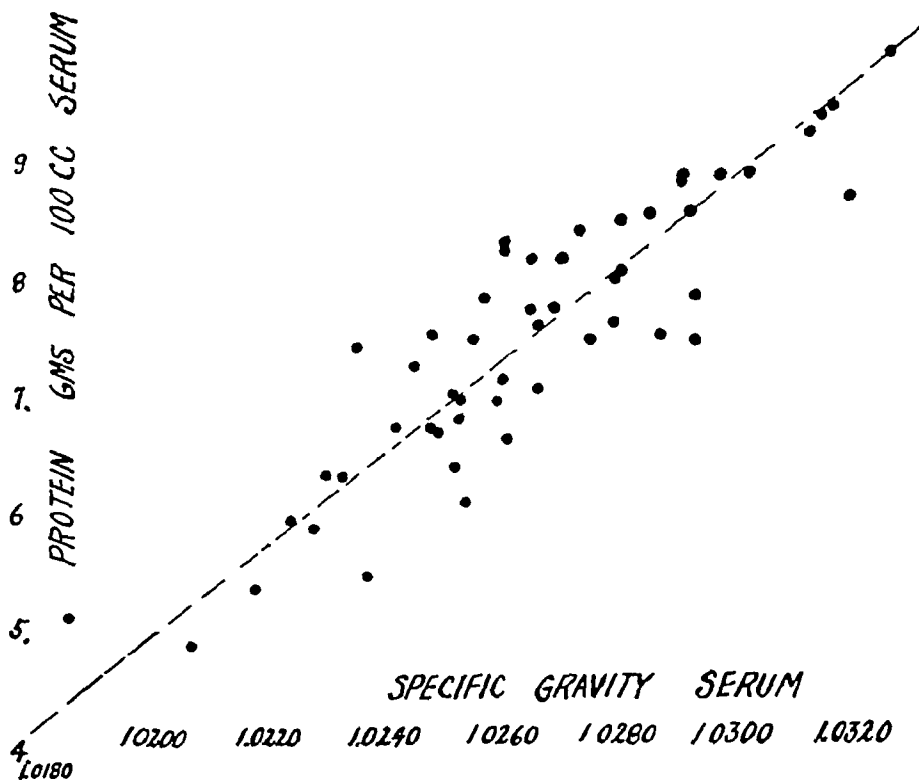
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*Changes in CO<sub>2</sub> content*

A recognizable though slight correlation between the concentration of CO<sub>2</sub> in the serum and the patients' temperatures is apparent in our cases as shown in graph 2 which includes also our cases of pneumonia. It was found by Stadie, Austin and Robinson (1925) that,

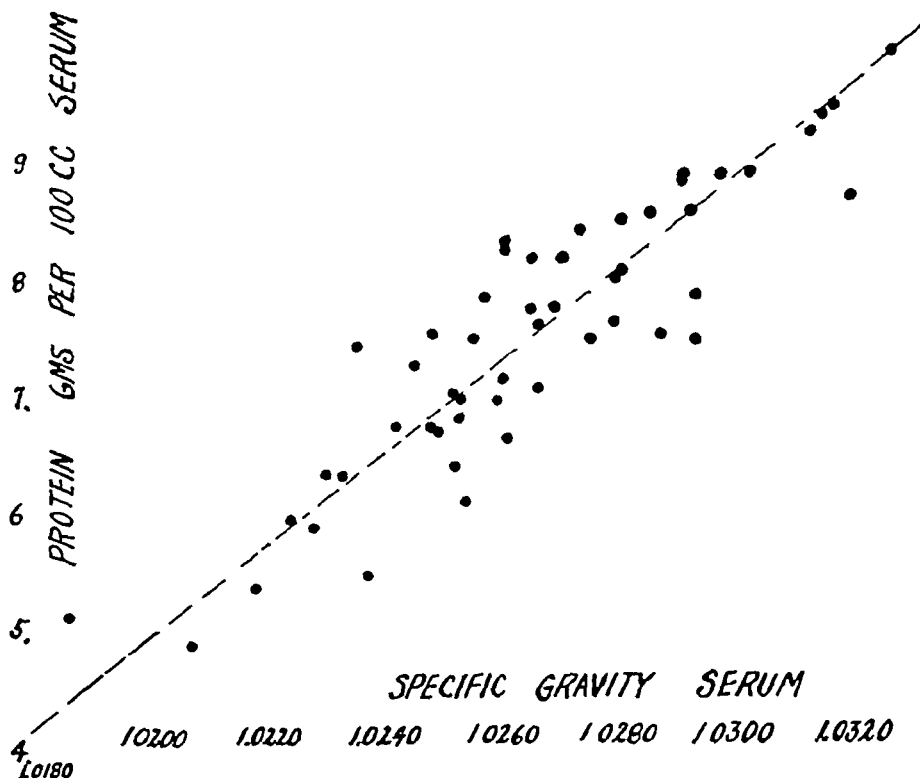


GRAPH 1 PROTEIN REFRACTOMETRICALLY OF ALL SERA, AGAINST SPECIFIC GRAVITY

at either constant CO<sub>2</sub> tension or constant pH, an elevation of the temperature lowers the carbon dioxide capacity about 1 mM for every 4.6°F. If the body temperature at the time when the blood was withdrawn in our cases be plotted as ordinate, and the CO<sub>2</sub> content be plotted as abscissae, it will be seen in graph 2 that the general trend of the CO<sub>2</sub> content was toward fall of CO<sub>2</sub> content with rise

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Reduction in bicarbonate occurred in certain individuals but was not clearly characteristic of any of these groups

Reduction in refractive index was observed in the chronic glomerulonephritics. A tendency to abnormal variations, sometimes high, sometimes low in refractive index was observed in the other pathologic cases

Elevation of the temperature was generally associated with a lowered CO<sub>2</sub> content. This was greater than could be accounted for by the change in base bound by protein with change in temperature and must be attributed either to acidosis or to hyperpnea

The series as a whole and the case of mercurial poisoning in particular suggest the readiness with which chloride is reduced in the serum to make way for other anions

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*Case A 16 (1728)* Age 19, white male Admitted March 25, 1927 Left pleural effusion following a cold three weeks before admission Fluid aspirated four times in first week of hospitalization, a total of 2600 cc. A pure culture of *streptococcus hemolyticus* was obtained from the fluid, no tubercle bacilli were found Temperature 98.2 to 102.3, leucocyte count 10,000 to 34,000

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*Case A 18 (4951)* Age 28, white, female Admitted February 16, 1927 Eclampsia developing at term Blood pressure 140 systolic, 100 diastolic Blood urea nitrogen 33 mgm per 100 cc Blood taken for analysis following the eighth convulsion and while in coma

*Case A 19 (S-100)* Age 38, white, male Admitted to hospital May 22, 1927, and discharged July 4, 1927 On May 22nd the patient took five large bichloride of mercury tablets Twenty minutes later he was given milk and in one hour he had emesis after taking six raw eggs On admission to the hospital two hours after taking the poison, he was given gastric lavage At this time he had developed abdominal cramps and diarrhea The patient was completely anuric from the time of admission until May 28th during which time he received from 3 to 6 liters of fluid daily From May 28th to June 6th the urine output varied from 400 to 750 cc daily and contained a trace of albumin, occasional casts, and red blood cells From June 8th until the day he was discharged the urine output varied from 400 to 3750 cc averaging approximately 1200 cc and contained no casts, a trace of albumin and, after June 13th, sugar in traces Phthalein test on June 30th showed excretion of 1 per cent in two hours Edema of the face was observed on day of admission It became more marked and generalized on May 26th and had disappeared by June 2nd On May 24th the patient had convulsions and was irrational, becoming rational two days later The eye grounds showed no hemorrhages, exudates, nor choking of discs Daily blood urea nitrogen determinations increased steadily from 43 mgm per 100 cc. on May 23rd to 247 mgm on June 11th and then decreased gradually to 85 mgm on July 2nd

*Case A 20 (815)* Age 39, colored male Admitted February 4, 1927 Died February 26, 1927 during a convulsion Diagnosis Chronic glomerulo-nephritis with failing circulation Blood pressure—220 systolic, 110 diastolic Fixation of specific gravity Phthalein excretion 5 per cent in first hour, less than 5 per cent in second hour Blood urea nitrogen 120 to 300 mgm per 100 cc Blood creatinin 13 to 16 mgm per 100 cc Hemoglobin 55 per cent

*Case A 21 (1912)* Age 42, white, male Admitted April 5, 1927 Broncho pneumonia with subacute nephritis Patient was admitted slightly delirious, complaining chiefly of pain in the left knee The left patella had been fractured three days previously The patient gave a history of nocturia four or five times a night during the past month His blood pressure was 124/72 Heart was slightly

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decompensation The patient was orthopneic There were petechiae over the trunk and right arm Blood pressure 96/48 Hemoglobin 65 per cent Leucocytes 12,000 Had received sodium salicylate and sodium bicarbonate for two days before blood was taken for analysis

*Case A 26 (1277)* Age 14, white, female Admitted March 1, 1927 Patient had had rheumatic fever each winter for the last four years and chorea during the past two years She had a marked mitral valvular lesion and coarse twitchings of all extremities At the time the blood was taken the patient was afebrile

*Case A 27 (1781)* Age 14, white, female Admitted March 28, 1927 Died April 18, 1927 Recurrent rheumatic fever with cardiac involvement for seven years Orthopneic, pallid, with large tender liver and spleen Blood pressure 124 systolic, 40 diastolic Hemoglobin 75 per cent Leucocytes 9,000 Developed pericardial friction, petechiae and increasing heart failure Diagnosis at autopsy Rheumatic pancarditis with aortic, mitral and tricuspid endocarditis, cardiac dilatation, chronic passive congestion of lungs, liver and spleen

*Case A 28 (703)* Age 24, colored, male Admitted January 28, 1927 Pulmonary abscess in right lower lobe with onset of symptoms one week before admission Culture of sputum showed a *Streptococcus viridans* predominating Leucocytes 13,000 to 20,000 Sputum 17 to 37 ounces daily

*Case A 29 (1859)* Age 60, white, female Admitted April 1, 1927 Carcinoma of head of pancreas, secondary metastases to liver and lungs intense jaundice Onset of symptoms with jaundice three months before admission

*Case A 30 (821)* Age 38, white, female Admitted February 4, 1927 Rheumatic pancarditis since adolescence, auricular fibrillation since 1915, marked heart failure, ascites and subcutaneous edema

*Case A 31 (1373)* Age 53, white, female Admitted February 7, 1927 Pernicious anemia of four years duration Hemoglobin 65 per cent, red blood cells 1.9 million, leucocytes 4,400 No free HCl in gastric contents Blood taken for analysis before transfusion

*Case A 32 (1337)* Age 16, white, male Admitted March 4, 1927 Pulmonary abscess in right upper lobe following tonsillectomy two weeks previously Through bronchoscope obtained a pure culture of *Micrococcus catarrhalis* Sputum 10 to 15 ounces daily

*Case A 33 (1346)* Age 28, colored, male Admitted March 5, 1927 Acute gangrenous perforating appendicitis with generalized peritonitis, onset March 1, operation March 5 Wassermann strongly positive From March 5 to 7 when blood was taken for analysis the patient received 180 cc of 5 per cent glucose and 2 per cent NaHCO<sub>3</sub> every three hours by rectum

*Case A 34 (1530)* Age 30 white, male Admitted March 15, 1927 Acute gangrenous perforating appendicitis with generalized peritonitis, operation on admission During following two days until blood was taken for analysis patient had received 100 cc physiological saline by hypodermoclysis and continuous enteroclysis with tap water

decompensation The patient was orthopneic There were petechiae over the trunk and right arm Blood pressure 96/48 Hemoglobin 65 per cent Leucocytes 12,000 Had received sodium salicylate and sodium bicarbonate for two days before blood was taken for analysis

*Case A 26 (1277)* Age 14, white, female Admitted March 1, 1927 Patient had had rheumatic fever each winter for the last four years and chorea during the past two years She had a marked mitral valvular lesion and coarse twitchings of all extremities At the time the blood was taken the patient was afebrile

*Case A 27 (1781)* Age 14, white, female Admitted March 28, 1927 Died April 18, 1927 Recurrent rheumatic fever with cardiac involvement for seven years Orthopneic, pallid, with large tender liver and spleen Blood pressure 124 systolic, 40 diastolic Hemoglobin 75 per cent Leucocytes 9,000 Developed pericardial friction, petechiae and increasing heart failure Diagnosis at autopsy Rheumatic pancarditis with aortic, mitral and tricuspid endocarditis, cardiac dilatation, chronic passive congestion of lungs, liver and spleen

*Case A 28 (703)* Age 24, colored, male Admitted January 28, 1927 Pulmonary abscess in right lower lobe with onset of symptoms one week before admission Culture of sputum showed a *Streptococcus viridans* predominating Leucocytes 13,000 to 20,000 Sputum 17 to 37 ounces daily

*Case A 29 (1859)* Age 60, white, female Admitted April 1, 1927 Carcinoma of head of pancreas, secondary metastases to liver and lungs intense jaundice Onset of symptoms with jaundice three months before admission

*Case A 30 (821)* Age 38, white, female Admitted February 4, 1927 Rheumatic pancarditis since adolescence, auricular fibrillation since 1915, marked heart failure, ascites and subcutaneous edema

*Case A 31 (1373)* Age 53, white, female Admitted February 7, 1927 Pernicious anemia of four years duration Hemoglobin 65 per cent, red blood cells 1.9 million, leucocytes 4,400 No free HCl in gastric contents Blood taken for analysis before transfusion

*Case A 32 (1337)* Age 16, white, male Admitted March 4, 1927 Pulmonary abscess in right upper lobe following tonsillectomy two weeks previously Through bronchoscope obtained a pure culture of *Micrococcus catarrhalis* Sputum 10 to 15 ounces daily

*Case A 33 (1346)* Age 28, colored, male Admitted March 5, 1927 Acute gangrenous perforating appendicitis with generalized peritonitis, onset March 1, operation March 5 Wassermann strongly positive From March 5 to 7 when blood was taken for analysis the patient received 180 cc of 5 per cent glucose and 2 per cent  $\text{NaHCO}_3$  every three hours by rectum

*Case A 34 (1530)* Age 30 white, male Admitted March 15, 1927 Acute gangrenous perforating appendicitis with generalized peritonitis, operation on admission During following two days until blood was taken for analysis patient had received 100 cc physiological saline by hypodermoclysis and continuous enteroclysis with tap water







classification from stimulant to depressant, but involved its use in heart disease and in such diseases as pneumonia in which many observers believed it to be beneficial

It soon appeared that in the new situation there were difficulties which it was impossible to ignore. Some of them it seemed possible to explore. They are questions such as these. Is the effect of digitalis in decreasing the volume output transient, as in Harrison and Leonard's dogs, or prolonged, as it appears to be in Burwell, Neighbors and Regen's patients, is it the same in animals with hearts of normal size and in animals the hearts of which are enlarged, does it make a difference whether the hearts are merely enlarged or does the presence of disease of the muscle also play a rôle in the final effect, does the presence of edema of the skin, tissues, and organs make a difference? If in all these situations digitalis behaves alike, is there perhaps a difference between dogs and man in the response to digitalis under any or all the heads which have been mentioned? And finally, in the interests of clearness, is the classification of digitalis as a depressant correct, and on which of its essential actions does the inference depend which places it in this category?

There is another matter of great interest which arises in connection with the studies of Harrison and Leonard. It concerns the definition of beneficial action and how its presence is to be ascertained. Shall beneficial action depend on the a priori assumption that it can be recognized and can be appraised in terms of one or another detailed effect of this drug, such as its effect on the blood pressure or the volume output or its effect on tone or on contraction or another of the many actions which it undoubtedly possesses? Or is it to depend on the net result of all these, on the general reaction of the whole man. The matter is one really of great difficulty in connection with the circulation. If digitalis, for instance, slowed the rate of the ventricles in auricular fibrillation but failed to relieve the patient permanently of whatever general disability affected him, would its use be continued even in the absence of a substitute? Examples like this may of course be multiplied. This one is suggested to illustrate the point at issue, namely, whether beneficial action can without searching analysis be equated with any one of the details of the action of an agent, especially when it is scarcely known whether

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To study the effect of digitalis upon contraction of cardiac muscle we made use of the method of photographing the motion of points of the heart's borders by casting shadows of these points made by roentgen rays upon moving films. We adapted for dogs the apparatus which Cohn and Stewart (1924) devised formerly

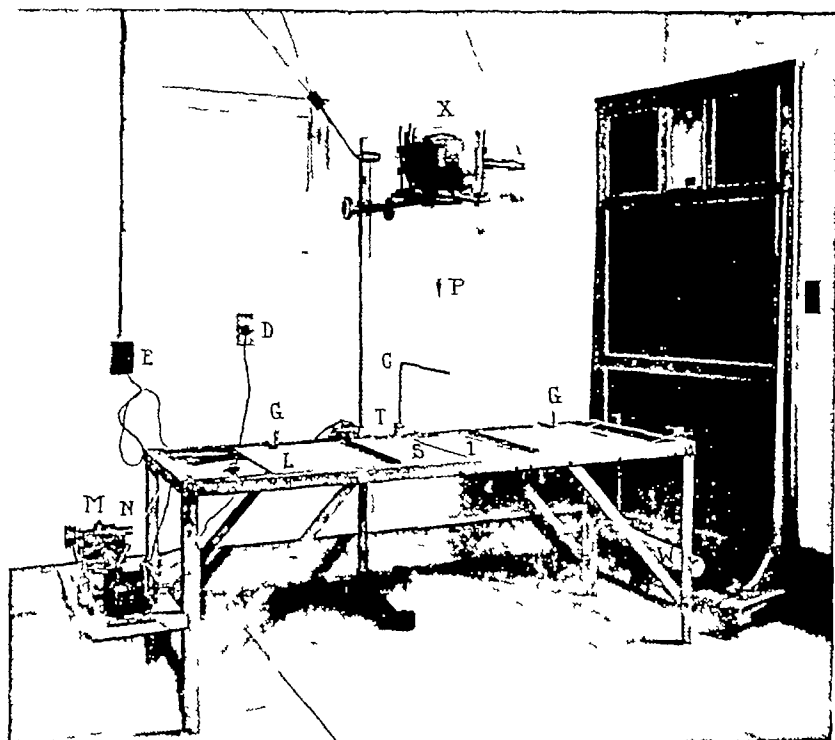


FIG 1 PHOTOGRAPH OF THE APPARATUS USED IN MAKING MOVING X-RAY PHOTOGRAPHS OF THE HEART

See figure 2 for a diagrammatic sketch of the apparatus. X, x-ray tube 34 inches from control film, P, plumb line for centering x-ray tube over slit S, C, rod to indicate location of slit S, T, electromagnetic time marker from Petzold clock, G, guide for dog board, D, switch to Petzold clock, E, current switch to motor M, L, lead screen, S, 0.5 cm slit in the lead screen, I, guides for control film, IV, counter-weight, N, cable for drawing moving film past the slit, M, motor.

for human beings. The photographic system instead of being vertical now functioned horizontally. The dogs lay on a proper board. This was placed upon a lead screen (fig 1 and 2, L) in which a transverse slit (fig 1 and 2, S) was cut 0.5 cm wide. Opposite the slit near one end a time recording lever (fig 1, T)

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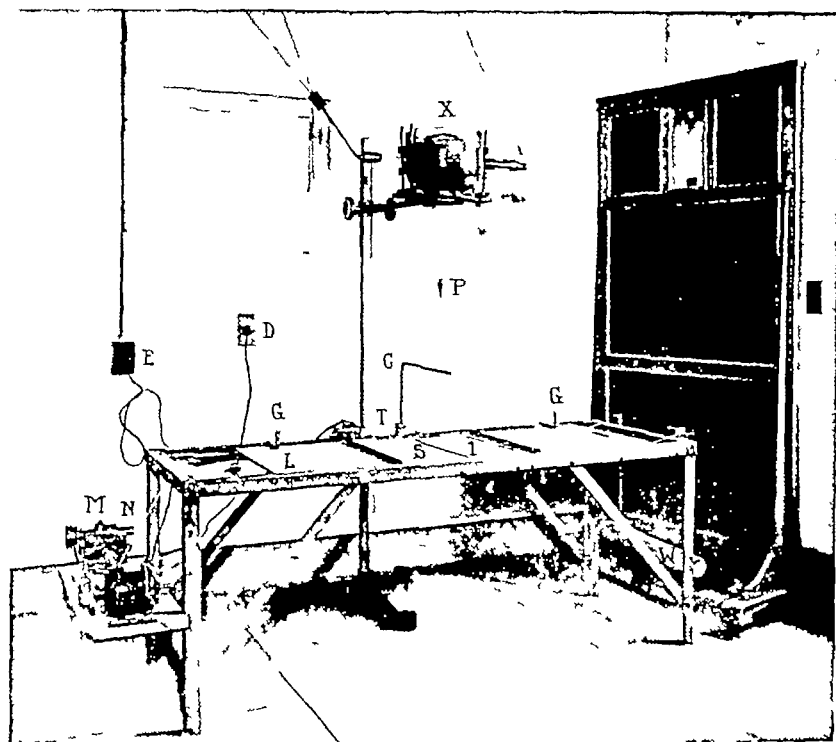


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## Effect of digitalis on cardiac output, cardiac

| Dog number and sex | Date        | Weight                      | O <sub>2</sub> content      |                             | Arterio-venous oxygen difference | Oxygen consumption | Cardiac output per min<br>ute | Cardiac output per cent<br>of initial | O <sub>2</sub> capacity | O <sub>2</sub> saturation† |              | Analysis of stationary films |                                   |   |
|--------------------|-------------|-----------------------------|-----------------------------|-----------------------------|----------------------------------|--------------------|-------------------------------|---------------------------------------|-------------------------|----------------------------|--------------|------------------------------|-----------------------------------|---|
|                    |             |                             | Arterial                    | Mixed venous                |                                  |                    |                               |                                       |                         | Arterial                   | Mixed venous | Heart area†                  | Heart area per<br>cent of initial | Rib or intercos-<br>tal space<br>photographed |
|                    |             |                             |                             |                             |                                  |                    |                               |                                       |                         |                            |              |                              |                                   |   |
| 1928               | kgm         | vol-<br>umes<br>per<br>cent | vol-<br>umes<br>per<br>cent | vol-<br>umes<br>per<br>cent | cc<br>per<br>min-<br>ute         | cc                 | per<br>cent                   | vol<br>umes<br>per<br>cent            | per<br>cent             | per<br>cent                | sq<br>cm     | per<br>cent                  |                                   |   |
| 257<br>Male        | January 31  | 12 4                        | 14 97                       | 12 12                       | 2 85                             | 109                | 3 820                         | 100 0                                 | 15 93                   | 92 7                       | 75 5         | 52 7                         | 100 0                             | 7th rib                                       |
|                    | February 1  |                             | 14 72                       | 10 68                       | 4 04                             | 95                 | 2 351                         | 61 5                                  | 16 49                   | 88 1                       | 64 3         | 47 7                         | 90 5                              | 7th rib                                       |
|                    | February 2  | 11 7                        | 14 87                       | 8 83                        | 6 04                             | 108                | 1 790                         | 46 8                                  | 16 33                   | 89 9                       | 53 5         | 43 8                         | 83 1                              | 7th rib                                       |
|                    | February 4  | 11 7                        | 13 51                       | 9 10                        | 4 41                             | 104                | 2 359                         | 61 7                                  | 15 42                   | 84 9                       | 62 0         | 48 2                         | 91 4                              | 7th rib                                       |
|                    | February 10 | 11 5                        | 12 57                       | 7 73                        | 4 84                             | 107                | 2 210                         | 57 8                                  | 13 44                   | 92 0                       | 56 8         | 47 7                         | 90 5                              | 7th rib                                       |
|                    |             | 12 0                        | 11 50                       | 8 41                        | 3 09                             | 111                | 3 592                         | 94 0                                  | 12 05                   | 93 8                       | 69 0         | 51 5                         | 97 7                              | 7th rib                                       |
| 258<br>Female      | February 6  | 16 0                        | 18 24                       | 15 28                       | 2 96                             | 139                | 4 696                         | 100 0                                 | 18 98                   | 95 0                       | 80 0         | 69 1                         | 100 0                             | 8th rib                                       |
|                    |             |                             | 18 31                       | 13 09                       | 5 22                             | 127                | 2 433                         | 51 8                                  | 19 34                   | 93 7                       | 66 9         | 56 7                         | 82 0                              | 8th rib                                       |
|                    | February 7  | 14 8                        | 18 56                       | 15 65                       | 2 91                             | 130                | 4 467                         | 95 1                                  | 19 42                   | 94 6                       | 80 1         | 60 0                         | 87 0                              | 8th rib                                       |
|                    | February 8  | 15 5                        | 16 47                       | 13 90                       | 2 57                             | 135                | 5 252                         | 111 8                                 | 17 25                   | 94 3                       | 79 4         |                              |                                   |   |
|                    | February 9  | 15 5                        | 15 42                       | 12 87                       | 2 55                             | 138                | 5 372                         | 114 4                                 | 16 15                   | 94 2                       | 79 1         | 63 0                         | 91 0                              | 8th rib                                       |
| 259<br>Male        | February 14 | 19 5                        | 21 26                       | 19 11                       | 2 15                             | 113                | 5 256                         | 100 0                                 | 22 12                   | 95 2                       | 85 9         | 78 8                         | 100 0                             | 6th rib                                       |
|                    |             |                             | 21 93                       | 17 60                       | 4 33                             | 114                | 2 633                         | 50 0                                  | 23 42                   | 92 8                       | 74 7         | 70 8                         | 89 8                              | 6th rib                                       |
|                    | February 15 | 17 5                        | 21 00                       | 16 08                       | 4 92                             | 116                | 2 357                         | 44 8                                  | 22 05                   | 94 3                       | 72 5         | 64 5                         | 81 1                              | 6th rib                                       |
|                    | February 17 | 17 5                        | 19 32                       | 15 90                       | 3 42                             | 125                | 3 655                         | 69 5                                  | 19 98                   | 95 7                       | 79 1         | 72 6                         | 92 1                              | 6th rib                                       |
|                    | February 21 | 17 7                        | 17 79                       | 16 16                       | 1 63                             | 119                | 7 300                         | 140 0                                 | 19 22                   | 91 6                       | 83 6         | 78 0                         | 98 8                              | 6th rib                                       |
| 261<br>Male        | February 23 | 12 8                        | 15 28                       | 10 55                       | 4 73                             | 122                | 2 580                         | 100 0                                 | 16 03                   | 94 1                       | 65 2         | 51 2                         | 100 0                             | 6th inter<br>space                            |
|                    |             |                             | 20 81                       | 7 30                        | 13 51                            | 112                | 829                           | 32 1                                  | 22 39                   | 92 1                       | 32 3         | 37 1                         | 72 4                              | 6th inter<br>space                            |
| 263<br>Male        | February 28 | 10 9                        | 21 38                       | 15 58                       | 5 80                             | 99                 | 1 707                         | 100 0                                 | 23 63                   | 90 5                       | 59 7         | 56 2                         | 100 0                             | 7th rib                                       |
|                    |             |                             | 23 88                       | 14 36                       | 9 52                             | 86                 | 902                           | 52 8                                  | 25 50                   | 92 9                       | 55 9         | 51 1                         | 90 9                              | 7th rib                                       |
|                    | February 29 | 10 3                        | 21 55                       | 15 96                       | 5 59                             | 95                 | 1 698                         | 99 6                                  | 21 93                   | 97 7                       | 72 3         | 50 4                         | 89 7                              | 7th rib                                       |
|                    | March 2     | 10 7                        | 18 55                       | 14 84                       | 3 71                             | 96                 | 2 588                         | 151 5                                 | 19 16                   | 95 7                       | 80 3         | 54 4                         | 96 8                              | 7th rib                                       |
|                    | March 8     | 10 8                        | 17 72                       | 14 02                       | 3 70                             | 97                 | 2 622                         | 153 5                                 | 18 26                   | 95 9                       | 76 2         | 57 4                         | 100 2                             | 7th rib                                       |
| 265<br>Male        | March 5     | 9 8                         | 16 24                       | 14 01                       | 2 23                             | 96                 | 4 305                         | 100 0                                 | 17 12                   | 93 7                       | 81 3         | 6th LS 39 8                  | 6th rib 40 2                      | 6th LS and<br>6th rib 100 0                   |
|                    |             |                             | 16 03                       | 9 26                        | 6 77                             | 98                 | 1 447                         | 33 6                                  | 17 40                   | 91 0                       | 52 6         | 34 8                         | 35 4                              | 87 5  |
|                    | March 6     | 9 4                         | 14 46                       | 10 89                       | 3 57                             | 99                 | 2 773                         | 64 4                                  | 15 38                   | 92 7                       | 70 1         | 37 7                         | 94 0                              | 6th rib                                       |
|                    | March 10    | 9 4                         | 14 12                       | 11 75                       | 2 27                             | 96                 | 4 190                         | 95 0                                  | 15 13                   | 92 0                       | 77 0         | 40 1                         | 40 2                              | 100 7   |
| 266<br>Male        | March 6     | 13 9                        | 16 42                       | 14 30                       | 2 12                             | 133                | 6 300                         | 100 0                                 | 17 35                   | 93 5                       | 81 8         | 58 3                         | 100 0                             | 6th rib                                       |
|                    | March 7     | 13 6                        | 14 89                       | 11 50                       | 3 39                             | 127                | 3 775                         | 60 0                                  | 16 09                   | 91 3                       | 69 2         | 51 2                         | 87 8                              | 6th rib                                       |
|                    | March 8     | 14 0                        | 14 99                       | 12 09                       | 2 90                             | 138                | 4 800                         | 76 2                                  | 15 74                   | 94 0                       | 76 2         | 53 6                         | 91 9                              | 6th rib                                       |
|                    | March 9     | 14 0                        | 14 40                       | 11 62                       | 2 78                             | 141                | 5 035                         | 80 5                                  | 15 52                   | 91 5                       | 74 2         | 56 6                         | 97 1                              | 6th rib                                       |
|                    |             |                             |                             |                             |                                  |                    |                               |                                       |                         |                            |              |                              |                                   |   |

\* V = vomited.

† Before calculating the oxygen saturations 0.2 and 0.1 volumes per cent (the amounts of oxygen in physical solution) were subtracted from the arterial and mixed venous contents respectively.

‡ These x ray photographs were taken at a distance of 34 inches.

§ Tincture digitalis unless otherwise indicated. I = intravenously M = by mouth.

*Effect of digitalis on cardiac outp*

| Dog number and sex | Date        | Weight | O <sub>2</sub> content      |                             | Arterio-venous oxygen difference | Oxygen consumption       | Cardiac output per minute | Cardiac output per cent of initial | O <sub>2</sub> capacity    | O <sub>2</sub> saturation† |              | Analysis of stations |                                |                   |                  |
|--------------------|-------------|--------|-----------------------------|-----------------------------|----------------------------------|--------------------------|---------------------------|------------------------------------|----------------------------|----------------------------|--------------|----------------------|--------------------------------|-------------------|------------------|
|                    |             |        | Arterial                    | Mixed venous                |                                  |                          |                           |                                    |                            | Arterial                   | Mixed venous | Heart area†          | Heart area per cent of initial |                   |                  |
|                    |             |        |                             |                             |                                  |                          |                           |                                    |                            |                            |              |                      |                                |                   |                  |
|                    | 1928        | kgm    | vol-<br>umes<br>per<br>cent | vol-<br>umes<br>per<br>cent | vol-<br>umes<br>per<br>cent      | cc<br>per<br>min-<br>ute | cc                        | per<br>cent                        | vol<br>umes<br>per<br>cent | per<br>cent                | per<br>cent  | sq cm                | per cent                       |                   |                  |
| 257<br>Male        | January 31  | 12 4   | 14 97                       | 12 12                       | 2 85                             | 109                      | 3 820                     | 100 0                              | 15 93                      | 92 7                       | 75 5         | 52 7                 | 100 0                          |                   |                  |
|                    |             |        | 14 72                       | 10 68                       | 4 04                             | 95                       | 2 351                     | 61 5                               | 16 49                      | 88 1                       | 64 3         | 47 7                 | 90 5                           |                   |                  |
|                    | February 1  | 11 7   | 14 87                       | 8 83                        | 6 04                             | 108                      | 1 790                     | 46 8                               | 16 33                      | 89 9                       | 53 5         | 43 8                 | 83 1                           |                   |                  |
|                    | February 2  | 11 7   | 13 51                       | 9 10                        | 4 41                             | 104                      | 2 359                     | 61 7                               | 15 42                      | 84 9                       | 62 0         | 48 2                 | 91 4                           |                   |                  |
|                    | February 4  | 11 5   | 12 57                       | 7 73                        | 4 84                             | 107                      | 2 210                     | 57 8                               | 13 44                      | 92 0                       | 56 8         | 47 7                 | 90 5                           |                   |                  |
|                    | February 10 | 12 0   | 11 50                       | 8 41                        | 3 09                             | 111                      | 3 592                     | 94 0                               | 12 05                      | 93 8                       | 69 0         | 51 5                 | 97 7                           |                   |                  |
| 258<br>Female      | February 6  | 16 0   | 18 24                       | 15 28                       | 2 96                             | 139                      | 4 696                     | 100 0                              | 18 98                      | 95 0                       | 80 0         | 69 1                 | 100 0                          |                   |                  |
|                    |             |        | 18 31                       | 13 09                       | 5 22                             | 127                      | 2 433                     | 51 8                               | 19 34                      | 93 7                       | 66 9         | 56 7                 | 82 0                           |                   |                  |
|                    | February 7  | 14 8   | 18 56                       | 15 65                       | 2 91                             | 130                      | 4 467                     | 95 1                               | 19 42                      | 94 6                       | 80 1         | 60 0                 | 87 0                           |                   |                  |
|                    | February 8  | 15 5   | 16 47                       | 13 90                       | 2 57                             | 135                      | 5 252                     | 111 8                              | 17 25                      | 94 3                       | 79 4         |                      |                                |                   |                  |
|                    | February 9  | 15 5   | 15 42                       | 12 87                       | 2 55                             | 138                      | 5 372                     | 114 4                              | 16 15                      | 94 2                       | 79 1         | 63 0                 | 91 0                           |                   |                  |
| 259<br>Male        | February 14 | 19 5   | 21 26                       | 19 11                       | 2 15                             | 113                      | 5 256                     | 100 0                              | 22 12                      | 95 2                       | 85 9         | 78 8                 | 100 0                          |                   |                  |
|                    |             |        | 21 93                       | 17 60                       | 4 33                             | 114                      | 2 633                     | 50 0                               | 23 42                      | 92 8                       | 74 7         | 70 8                 | 89 8                           |                   |                  |
|                    | February 15 | 17 5   | 21 00                       | 16 08                       | 4 92                             | 116                      | 2 357                     | 44 8                               | 22 05                      | 94 3                       | 72 5         | 64 5                 | 81 1                           |                   |                  |
|                    | February 17 | 17 5   | 19 32                       | 15 90                       | 3 42                             | 125                      | 3 655                     | 69 5                               | 19 98                      | 95 7                       | 79 1         | 72 6                 | 92 1                           |                   |                  |
|                    | February 21 | 17 7   | 17 79                       | 16 16                       | 1 63                             | 119                      | 7 300                     | 140 0                              | 19 22                      | 91 6                       | 83 6         | 78 0                 | 98 8                           |                   |                  |
| 261<br>Male        | February 23 | 12 8   | 15 28                       | 10 55                       | 4 73                             | 122                      | 2 580                     | 100 0                              | 16 03                      | 94 1                       | 65 2         | 51 2                 | 100 0                          |                   |                  |
|                    |             |        | 20 81                       | 7 30                        | 13 51                            | 112                      | 829                       | 32 1                               | 22 39                      | 92 1                       | 32 3         | 37 1                 | 72 4                           |                   |                  |
| 263<br>Male        | February 28 | 10 9   | 21 38                       | 15 58                       | 5 80                             | 99                       | 1 707                     | 100 0                              | 23 63                      | 90 5                       | 59 7         | 56 2                 | 100 0                          |                   |                  |
|                    |             |        | 23 88                       | 14 36                       | 9 52                             | 86                       | 902                       | 52 8                               | 25 50                      | 92 9                       | 55 9         | 51 1                 | 90 9                           |                   |                  |
|                    | February 29 | 10 3   | 21 55                       | 15 96                       | 5 59                             | 95                       | 1 698                     | 99 6                               | 21 93                      | 97 7                       | 72 3         | 50 4                 | 89 7                           |                   |                  |
|                    | March 2     | 10 7   | 18 55                       | 14 84                       | 3 71                             | 96                       | 2 588                     | 151 5                              | 19 16                      | 95 7                       | 80 3         | 54 4                 | 96 8                           |                   |                  |
|                    | March 8     | 10 8   | 17 72                       | 14 02                       | 3 70                             | 97                       | 2 622                     | 153 5                              | 18 26                      | 95 9                       | 76 2         | 57 4                 | 100 2                          |                   |                  |
| 265<br>Male        | March 5     | 9 8    | 16 24                       | 14 01                       | 2 23                             | 96                       | 4 305                     | 100 0                              | 17 12                      | 93 7                       | 81 3         | 6th I.S.<br>39 8     | 6th rib<br>40 2                | 6th I.S.<br>100 0 | 6th rib<br>100 0 |
|                    |             |        | 16 03                       | 9 26                        | 6 77                             | 98                       | 1 447                     | 33 6                               | 17 40                      | 91 0                       | 52 6         | 34 8                 | 35 4                           | 87 5              | 88 3             |
|                    | March 6     | 9 4    | 14 46                       | 10 89                       | 3 57                             | 99                       | 2 773                     | 64 4                               | 15 38                      | 92 7                       | 70 1         | 37 7                 |                                | 94 0              |                  |
|                    | March 10    | 9 4    | 14 12                       | 11 75                       | 2 27                             | 96                       | 4 190                     | 95 0                               | 15 13                      | 92 0                       | 77 0         | 40 1                 | 40 2                           | 100 7             | 100 0            |
| 266<br>Male        | March 6     | 13 9   | 16 42                       | 14 30                       | 2 12                             | 133                      | 6 300                     | 100 0                              | 17 35                      | 93 5                       | 81 8         | 58 3                 |                                | 100 0             |                  |
|                    |             |        |                             |                             |                                  |                          |                           |                                    |                            |                            |              |                      |                                |                   |                  |
|                    | March 7     | 13 6   | 14 89                       | 11 50                       | 3 39                             | 127                      | 3 775                     | 60 0                               | 16 09                      | 91 3                       | 69 2         | 51 2                 |                                | 87 8              |                  |
|                    | March 8     | 14 0   | 14 99                       | 12 09                       | 2 90                             | 138                      | 4 800                     | 76 2                               | 15 74                      | 94 0                       | 76 2         | 53 6                 |                                | 91 9              |                  |
|                    | March 9     | 14 0   | 14 40                       | 11 62                       | 2 78                             | 141                      | 5 035                     | 80 5                               | 15 52                      | 91 5                       | 74 2         | 56 6                 |                                | 97 1              |                  |

\* V = vomited.

† Before calculating the oxygen saturations 0.2 and 0.1 volumes per cent (the amounts of oxygen in physical solution) were subtracted from the arterial and mixed venous contents respectively.

‡ These x-ray photographs were taken at a distance of 34 inches.

§ Tincture digitalis unless otherwise indicated. I = intravenously. M = by mouth.

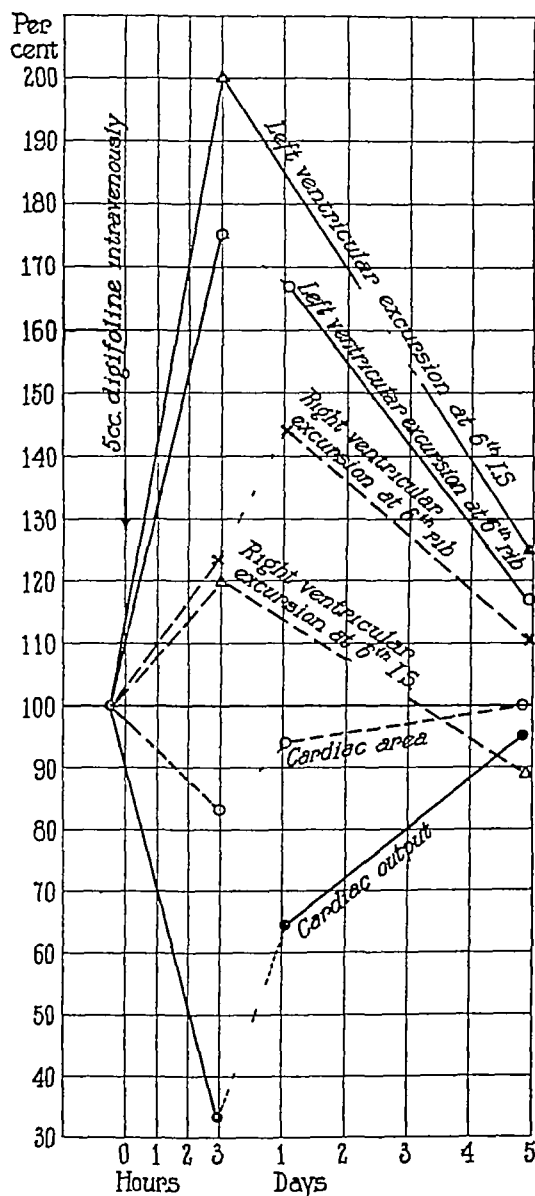


FIG 3 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 265

Photographs were made at the 6th interspace as well as at the level of the 6th rib. As the effect of digitalis wore off cardiac output, cardiac size and extent of ventricular excursions returned simultaneously toward normal.

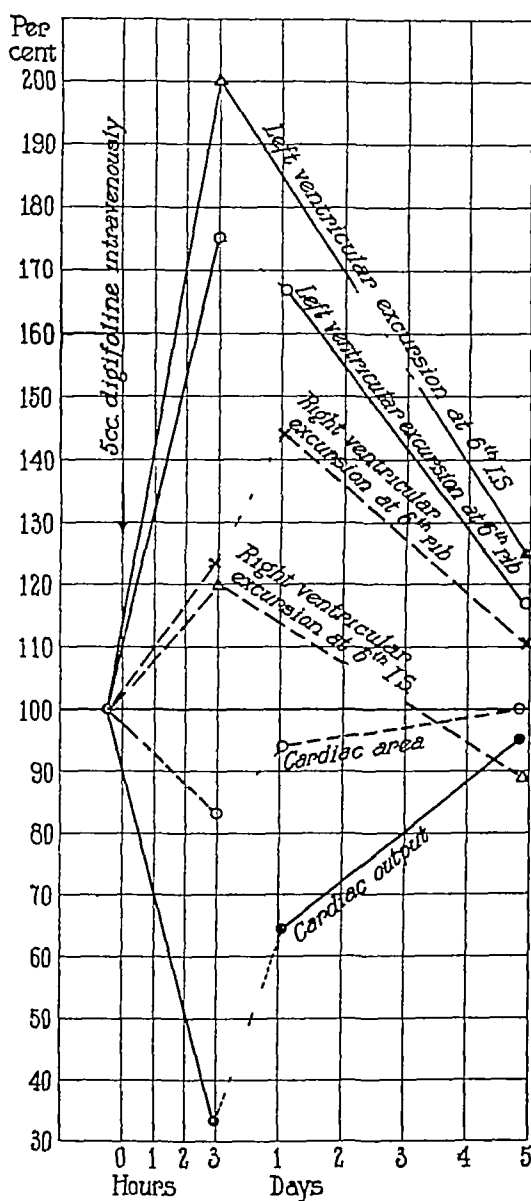
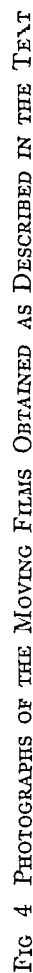


FIG 3 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 265

Photographs were made at the 6th interspace as well as at the level of the 6th rib. As the effect of digitalis wore off cardiac output, cardiac size and extent of ventricular excursions returned simultaneously toward normal.





Below each photograph is placed the corresponding tracing made from the original films of the excursions of the right and left ventricles respectively. The photographs are reduced to one-fourth of their natural size.



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Cohn (Cohn) found that the dose for cats must be multiplied by the factor 1.16 to arrive at a comparable quantity for dogs. We have accordingly injected this amount. To several dogs we administered digitoline (Ciba) intravenously for the sake of comparison with the experiments of Harrison and Leonard (1926). Of this preparation we injected 0.5 cc per kilogram of body weight (Harrison and Leonard (1926), Pardee (1925)). To one dog we gave digitan (Merck) 1.0 gram by mouth. The same phenomena resulted irrespective of the preparation that was administered.

#### OBSERVATIONS

In 7 dogs we have complete data of the effect of giving digitalis on cardiac output, cardiac size and ventricular contraction (excursions).

*The effect of digitalis on cardiac output.* In dog 257 the cardiac output was 3820 cc per minute (table 1, fig. 5). Two and one-half hours after tincture of digitalis 2.8 cc had been given intravenously the output fell to 2351 cc per minute, there occurred, that is to say, a decrease to 61.2 per cent of the initial output. Later, at 26½ hours, the output fell still further to 1790 cc, equal to 46.8 per cent only of the output at the beginning. On the second day there was a change. The output increased to 2359 cc and in 10 days returned to 3592 cc, that is to say, to 94 per cent of the initial value. In this dog then there was after the administration of digitalis a decrease in cardiac output within 2½ hours which reached a maximum 24 hours later. The return to normal, though not complete, took place at the end of 10 days.

The results were similar in the other 6 dogs (table 1, figs. 3 and 6), with this exception, namely that in 3 dogs (dog 258 (fig. 6), dog 259 and dog 263) the output, following the initial decrease actually became greater than it had been at first. This observation will be discussed later at greater length. In general, though, the output decreased uniformly 2½ to 3 hours after the administration of digitalis, but the maximum was usually delayed until 24 hours later. It varied between 34 and 62 per cent of the initial value (table 1). Later the cardiac output returned toward normal (dog 261, dog 265 (fig. 3) and dog 266) or exceeded this value (dog 258 (fig. 6), dog 259 and dog 263). The changes in output occurred irrespective of changes

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#### OBSERVATIONS

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in heart rate (recorded electrocardiographically) though this was found usually to have decreased 2 to 3 hours after administration. Later the rate returned to what it was at the outset of the experiment.

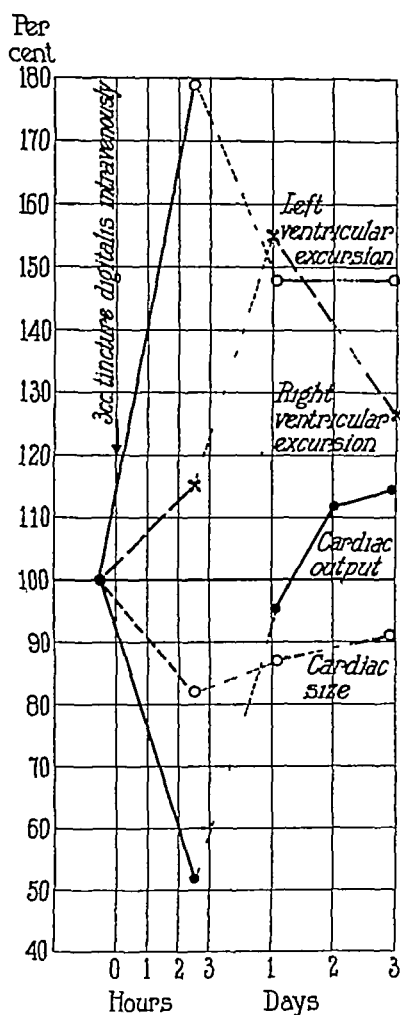


FIG 6 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 258

In this instance, after the preliminary decrease, the cardiac output increased and overshot the initial measurement even though the heart was smaller than it was in the beginning. This result is attributed to the fact that the height of the ventricular excursions continued greater than it was in the initial measurements.

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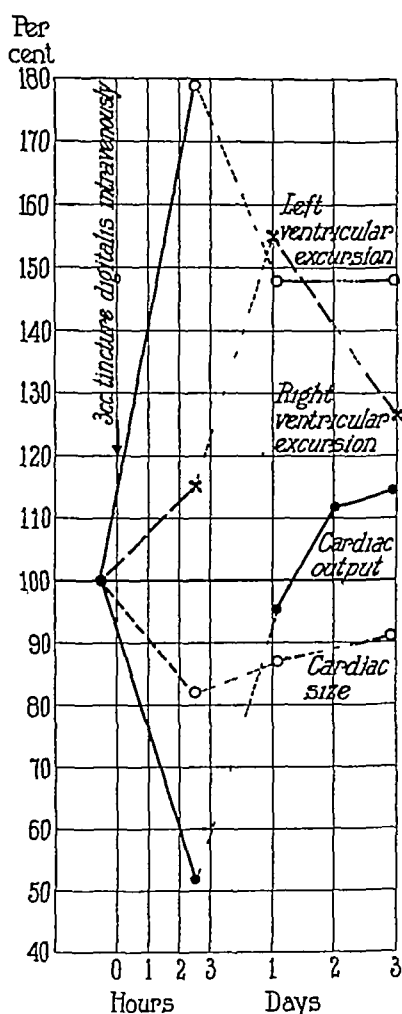


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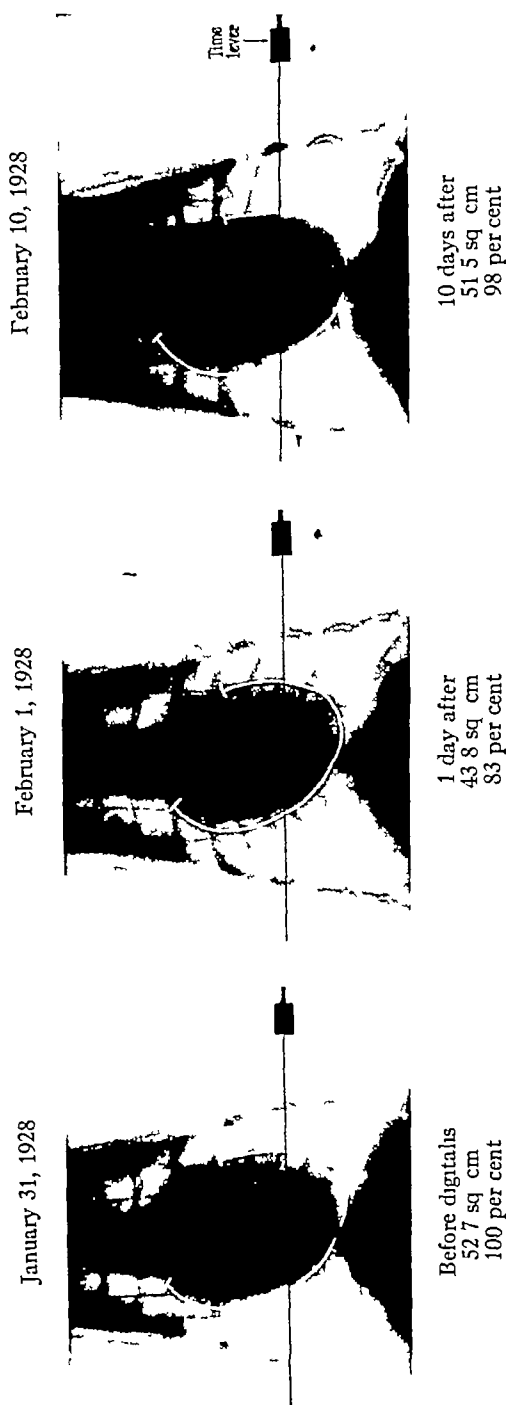


FIG 7 PHOTOGRAPHS WHICH SHOW THE EFFECT OF GIVING DIGITALIS ON THE SIZE OF THE HEART OF DOG 257

The x-ray photographs were taken on the days indicated. Below each photograph is recorded the area of the heart. The photographs are reduced to one fourth of their natural size.

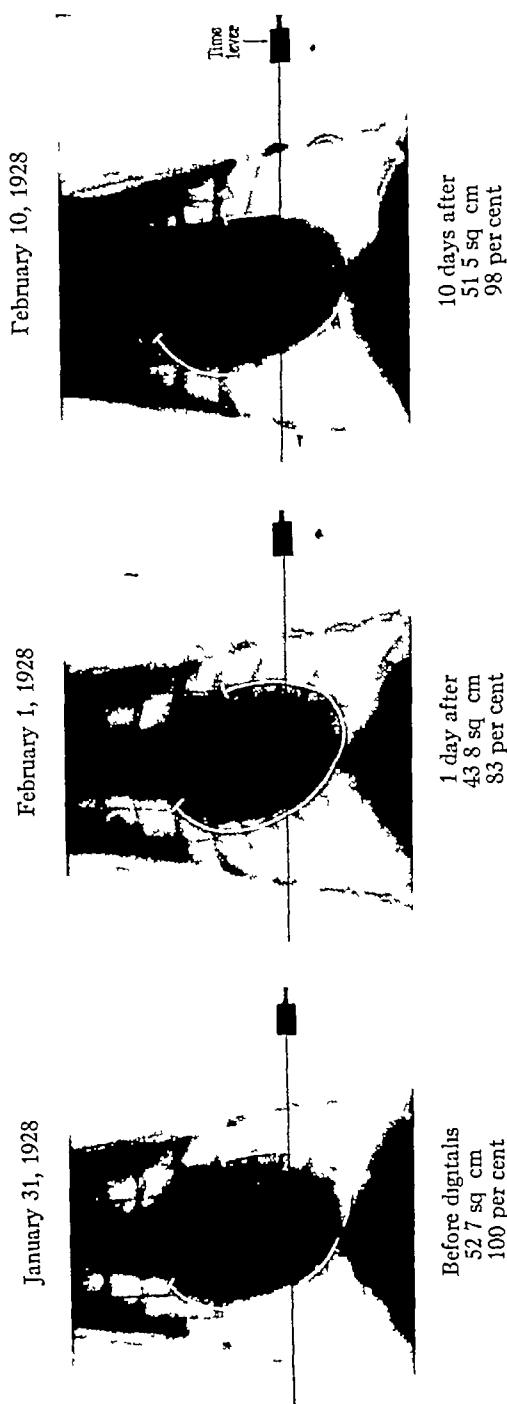


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The x-ray photographs were taken on the days indicated. Below each photograph is recorded the area of the heart. The photographs are reduced to one fourth of their natural size.





TABLE 3  
*Effect of injecting digitalis upon cardiac output and cardiac size in normal dogs*

| Dog number and sex | Date              | Weight<br>kgm | O <sub>2</sub> content |              | Arterio-venous oxygen differ-<br>ence | Oxygen consumption |                 | Cardiac output per minute |          | Change in cardiac output* |          | O <sub>2</sub> capacity |          | O <sub>2</sub> saturation† |          | Heart area†<br>sq cm | Change in heart area* |      | Rhythm | Heart rate (electro-cardiogram)<br>per minute | Digitalis given intravenously‡<br>cc | Time after injection of digitalis<br>hours     | Summary of effect on electro-<br>cardiogram          |
|--------------------|-------------------|---------------|------------------------|--------------|---------------------------------------|--------------------|-----------------|---------------------------|----------|---------------------------|----------|-------------------------|----------|----------------------------|----------|----------------------|-----------------------|------|--------|---|--------------------------------------|--|--|
|                    |                   |               | Arterial               | Mixed venous |                                       | cc                 | per min-<br>ute | per cent                  | per cent | per cent                  | per cent | per cent                | per cent | per cent                   | per cent |                      | per cent              |      |        |   |                                      |  |  |
| 253<br>Male        | November 29, 1927 | 12.5          | 15.61                  | 12.61        | 3.00                                  | 122                | 4.066           | 100                       | 16.37    | 94                        | 2.76     | 5.44                    | 7.100    | 0                          |          |                      |                       | N.R. | 110    |   |                                      |  |  |
|                    | November 30, 1927 | 11.8          | 16.31                  | 11.72        | 4.59                                  | 119                | 2.592           | 64                        | 16.17    | 47                        | 92       | 2.66                    | 6.37     | 2.83                       | 0        | -20                  | 0                     | N.R. | 90     | 3.0   | 2                                    | Decrease in ventricular rate change in T waves |  |
|                    | December 3, 1927  | 11.5          | 13.75                  | 9.71         | 4.04                                  | 132                | 3.267           | 80                        | 16.17    | 47                        | 92       | 2.66                    | 6.37     | 2.83                       | 0        | -17                  | 0                     | N.R. | 150    |   |                                      |  |  |
| 254<br>Male        | November 28, 1927 | 14.8          | 16.02                  | 13.22        | 2.80                                  | 120                | 4.285           | 100                       | 16.40    | 96                        | 4.80     | 0.43                    | 6.100    | 0                          |          |                      |                       | N.R. | 140    |   |                                      |  |  |
|                    |                   | 17.2          | 15.11                  | 9.6          | 5.29                                  | 124                | 2.344           | 55                        | 17.79    | 95                        | 8.66     | 8.35                    | 7.82     | 0                          | -18      | 0                    | Vent. tach            | 230  | 3.3    | 2   | Vent. tach, change in T-waves        |  |  |
|                    | November 29, 1927 | 13.3          | 15.50                  | 11.16        | 4.34                                  | 114                | 2.627           | 61                        | 16.42    | 93                        | 2.67     | 4.38                    | 6.88     | 5                          | -11      | 5                    | N.R.                  | 130  |        |   |                                      |  |  |
| 252<br>Female      | December 2, 1927  | 13.6          | 14.18                  | 11.63        | 2.55                                  | 123                | 4.823           | 112                       | 12.14    | 69                        | 95       | 2.78                    | 4.43     | 2.99                       | 0        | -1                   | 0                     | N.R. | 100    |   |                                      |  |  |
|                    | December 6, 1927  | 16.8          | 20.50                  | 17.58        | 2.92                                  | 181                | 6.195           | 100                       | 20.54    | 98                        | 8.85     | 2.56                    | 5.100    | 0                          |          |                      |                       | N.R. | 140    |   |                                      |  |  |
|                    | December 7, 1927  | 20.1          | 16.15                  | 8.1          | 4.35                                  | 175                | 4.023           | 65                        | 20.35    | 20                        | 43       | 97                      | 5.77     | 0.46                       | 7.83     | 0                    | -17                   | 0    | N.R.   | 90  | 3.8                                  | 2  | Ventricular rate decreased, slight change in T waves |
|                    | December 10, 1927 | 17.0          | 17.05                  | 14.02        | 3.03                                  | 172                | 5.670           | 91                        | 17.20    | 74                        | 94       | 7.77                    | 9.50     | 4.89                       | 0        | -11                  | 0                     | N.R. | 150    |   |                                      |  |  |
|                    |                   |               |                        |              |                                       |                    |                 |                           |          |                           |          |                         |          |                            |          |                      |                       | N.R. | 160    |   |                                      |  |  |

## SUMMARY

Following the administration of digitalis to normal dogs in so-called therapeutic amounts the following effects were observed (1) the form of the T-wave in the electrocardiogram changed, (2) the cardiac output *decreased*, (3) the size of the heart *decreased*, (4) the height of ventricular excursions *increased*. When digitalis was excreted all these measurements returned toward normal.

## DISCUSSION

We have demonstrated then that following the administration of digitalis to normal dogs the cardiac output and the cardiac size *decreased*, but the extent of ventricular contraction on the other hand *increased*. In what way are these observations to be connected in analyzing the effect of digitalis on cardiac output? In our early experiments (Cohn and Stewart, 1928a) the six to which reference has just been made and in which cardiac output and cardiac size alone were correlated, there was close agreement between the two, when the cardiac size decreased the cardiac output decreased, as we thought, necessarily. But that the influence of digitalis on the two functions was distinct and separable became apparent when the effect of digitalis began to wear off. When the size of the heart began to increase, the output sometimes increased more than it should have done were size the only factor involved (dogs 254 and 255, table 3). Why this was so was difficult at first to explain, but the reason became evident as we thought, when we began to take into account the effect of the drug on contraction. There was ample reason to anticipate a striking effect on this function based on evidence gained by many other observers from experiments on animals that had been operated on. What the effect is in intact animals to which no anesthetic had been given was however unknown. The method of the moving film employed in this study permitted an answer to this question, ventricular contraction increases in the intact as it does in the animal which has been operated upon.

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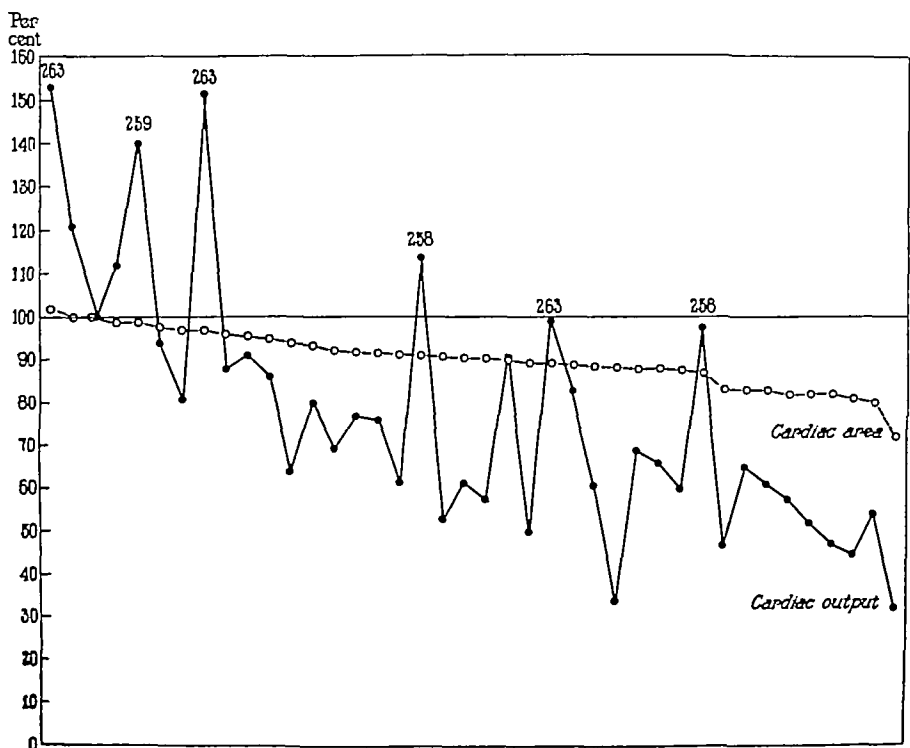


FIG 8 SHOWING THE CORRELATION BETWEEN CARDIAC SIZE AND CARDIAC OUTPUT

For explanation see the text

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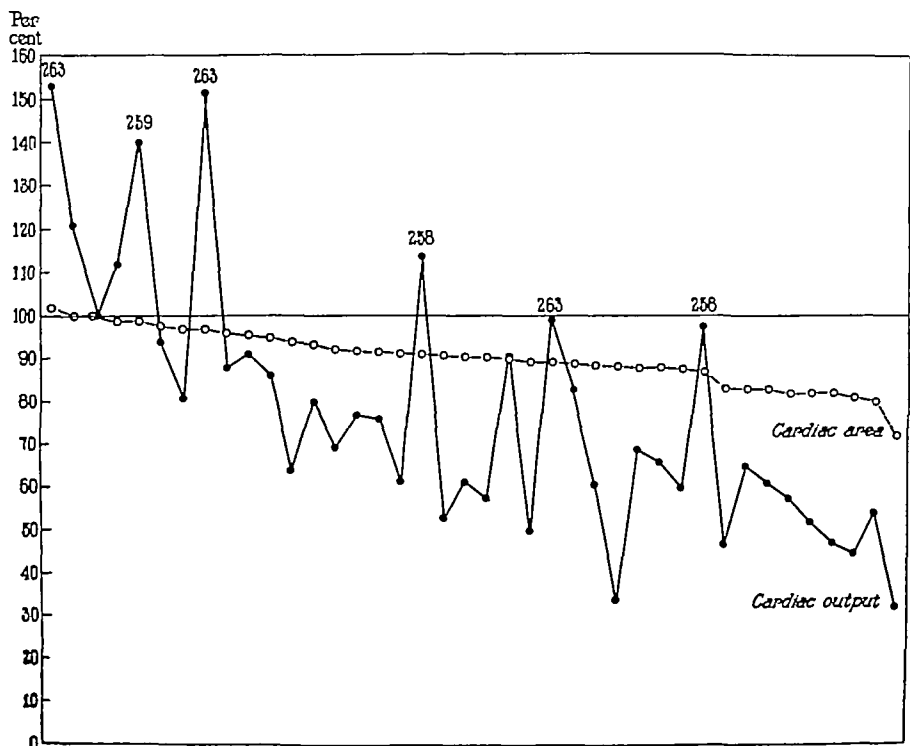


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## SUMMARY

The effect of therapeutic doses of digitalis given intravenously and by mouth upon the circulation of normal dogs has been studied. It was found that

1 Changes in T-waves of the electrocardiograms were constantly observed

2 The heart rate always slowed 2 to 3 hours after giving digitalis unless an abnormal rhythm developed. In 24 hours the rate was like the initial count

3 The cardiac area decreased

4 The ventricular excursions increased

5 The cardiac output always decreased at first, but might later increase

6 These effects were at a maximum 2 to 24 hours after the administration of the drug

7 As the effect of digitalis wore off the cardiac output, cardiac size and ventricular excursions returned to normal. The cardiac output often became greater than the initial value

## CONCLUSIONS

Digitalis within the first 24 hours decreases the cardiac output of normal dogs. The cardiac output which obtains at any later instant is the net result of the working of two opposing factors. The first of these effects increases cardiac tone and results in decrease in the size of the heart. It is due to this action that cardiac output tends to decrease. The second effect increases ventricular contraction and tends to increase cardiac output. If cardiac size is not smaller than a critical value, increase in ventricular contraction overbalances decrease in size so that cardiac output increases beyond the beginning value.

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## MATERIAL

The dogs which were studied were operated on  $2\frac{1}{6}$  to  $4\frac{1}{2}$  years ago. Evidence of the lesions which were then created were still present at the time of these experiments (table 1). Complete data concerning the operations in these animals will be published later (Stewart). A brief description only of the method used in operating on the valves need be given. Under ether and under aseptic conditions the left auricular appendage was exposed and incised. A cardioscope<sup>1</sup> was then inserted through this opening and placed so that the leaflets of

TABLE 1  
*Enlargement of the heart following induction of artificial mitral insufficiency in dogs*

| Dog number | Area of heart*<br>before operation | Area of heart*<br>after operation | Time since<br>operation | Increase in heart<br>area |
|------------|------------------------------------|-----------------------------------|-------------------------|---------------------------|
|            | <i>sq cm</i>                       | <i>sq cm</i>                      | <i>years</i>            | <i>per cent</i>           |
| 155        | 56.1                               | 66.1                              | $2\frac{1}{2}$          | 18                        |
| 158        | 46.4                               | 84.3                              | $2\frac{1}{2}$          | 82                        |
|            |                                    | 90.2                              | $3\frac{1}{2}$          | 94                        |
| 161        | 46.0                               | 71.4                              | $2\frac{1}{2}$          | 55                        |
|            |                                    | 81.2                              | $3\frac{1}{2}$          | 77                        |
| 162        | 55.0                               | 65.8                              | $2\frac{1}{2}$          | 20                        |
|            |                                    | 66.9                              | $3\frac{1}{2}$          | 22                        |
| 171        | 50.3                               | 62.3                              | $2\frac{1}{2}$          | 24                        |
| 90         | 43.0                               | 45.3                              | $4\frac{1}{2}$          | 5                         |

\* The x ray photographs were made at a distance of 2 meters

the mitral valve were brought into view. The leaflet could then be cut under direct vision. Development of a marked systolic thrill was

<sup>1</sup> The cardioscope which we used was designed with the assistance of Mr R. Wappler, and was made for us by the Wappler Electric Company, Long Island City, New York. The idea of cutting the valves of the heart under direct vision was suggested to us by the preliminary report of Allen and Graham (1922). As complete data for the construction of their instrument was not available at the time, we devised this new instrument. The optical system is similar to that used in cystoscopes. We are much indebted to Doctors Graham and Allen for valuable aid in learning their methods and desire to express our thanks to them for their courtesy.

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## Effect of digitalis on cardiac output, cardiac size and ventricular

| Dog number and sex | Date           | Weight | O <sub>2</sub> content |                  | Arterio venous oxygen difference | Oxygen consumption | Cardiac output per minute | Cardiac output per cent of initial | Change in cardiac output* | O <sub>2</sub> capacity | O <sub>2</sub> saturation |              |
|--------------------|----------------|--------|------------------------|------------------|----------------------------------|--------------------|---------------------------|------------------------------------|---------------------------|-------------------------|---------------------------|--------------|
|                    |                |        | Arterial               | Mixed venous     |                                  |                    |                           |                                    |                           |                         | Arterial                  | Mixed venous |
|                    |                | kgm    | volumes per cent       | volumes per cent | volumes per cent                 | cc per minute      | cc                        | per cent                           | per cent                  | vol-umes per cent       | per cent                  | per cent     |
| 162 Female         | May 23, 1927   | 17 1   | 18 84                  | 16 73            | 2 11                             | 106                | 5,024                     | 100 0                              |                           | 19 80                   | 94 1 8                    |              |
|                    |                |        | 21 97                  | 17 00            | 4 97                             | 106                | 2,133                     | 42 0                               | -58 0                     | 22 00                   | 98 9 7                    |              |
|                    | May 24, 1927   |        | 19 04                  | 16 42            | 2 62                             | 111                | 4,237                     | 84 0                               | -16 0                     | 20 03                   | 94 1 8                    |              |
|                    | May 25, 1927   |        | 18 86                  | 15 10            | 3 76                             | 122                | 3,249                     | 64 0                               | -36 0                     | 19 78                   | 94 3 7                    |              |
|                    | May 27, 1927   |        | 16 53                  | 13 86            | 2 67                             | 119                | 4,459                     | 89 0                               | -11 0                     | 16 80                   | 97 2 8                    |              |
|                    | June 1, 1927   |        | 13 75                  | 11 96            | 1 74                             | 124                | 7,084                     | 120 0                              | +20 0                     | 14 91                   | 98 5 8                    |              |
|                    | March 19, 1928 | 17 4   | 15 51                  | 13 77            | 1 74                             | 116                | 6,663                     | 100 0                              |                           | 16 04                   | 95 5 8                    |              |
|                    |                |        | 18 43                  | 13 46            | 4 97                             | 109                | 2,163                     | 32 9                               | -67 1                     | 20 02                   | 91 1 6                    |              |
|                    | March 20, 1928 | 16 5   | 17 31                  | 13 55            | 3 76                             | 109                | 2,900                     | 43 5                               | -56 5                     | 18 50                   | 92 5 1                    |              |
|                    | March 21, 1928 | 15 9   | 15 70                  | 11 79            | 3 91                             | 106                | 2,710                     | 41 3                               | -58 7                     | 16 45                   | 94 2 7                    |              |
|                    | March 29, 1928 | 14 5   | 14 05                  | 10 08            | 3 97                             | 98                 | 2,468                     | 100 0                              |                           | 14 98                   | 92 4 6                    |              |
|                    |                |        | 15 42                  | 9 69             | 5 73                             | 95                 | 1,657                     | 67 2                               | -32 8                     | 16 48                   | 92 3 3                    |              |
|                    | March 30, 1928 | 13 5   | 14 27                  | 10 08            | 4 19                             | 96                 | 2,292                     | 92 9                               | -7 1                      | 15 65                   | 90 0 6                    |              |
|                    | April 2, 1928  | 13 6   | 12 76                  | 8 86             | 3 90                             | 98                 | 2,538                     | 102 7                              | +2 7                      | 13 99                   | 89 8 6                    |              |
| 161 Male           | June 6, 1927   | 14 8   | 17 11                  | 15 34            | 1 77                             | 154                | 8,700                     | 100 0                              |                           | 17 94                   | 94 2 8                    |              |
|                    |                |        | 18 86                  | 14 58            | 4 28                             | 144                | 3,365                     | 38 0                               | -62 0                     | 19 82                   | 94 1 1                    |              |
|                    | June 7, 1927   |        | 18 82                  | 15 08            | 3 74                             | 148                | 3,959                     | 45 0                               | -55 0                     | 19 20                   | 96 9 1                    |              |
|                    | June 8, 1927   |        | 17 36                  | 12 99            | 4 37                             | 138                | 3,159                     | 36 0                               | -64 0                     | 18 10                   | 94 8 1                    |              |
|                    | June 10, 1927  |        | 14 76                  | 12 99            | 1 77                             | 133                | 7,514                     | 86 0                               | -14 0                     | 15 28                   | 96 7 8                    |              |

\* In this column, + indicates increase, and - decrease

† Before calculating the oxygen saturations 0.2 and 0.1 volume per cent (the amount of oxygen in physical solution) were subtracted from the arterial and mixed venous oxygen contents respectively

§ Tincture of digitalis unless otherwise indicated

|| N R = normal rhythm, A.F. = auricular fibrillation, V P C = ventricular premature contractions, A P C = auricular premature contractions, Vent. Par Tach = ventricular paroxysmal tachycardia, I = incomplete heart block, + P-R = conduction time increased

*Effect of digitalis on cardiac output, cardiac size and ventricular*

TAB

LE 1

contraction (excursion) in do

| Dog number and sex | Date           | Weight | O <sub>2</sub> content |              | Arterio venous oxygen difference | Oxygen consumption | Cardiac output per minute | Cardiac output per cent of initial | Change in cardiac output* | O <sub>2</sub> capacity | O <sub>2</sub> saturation |              | Analysis of stationary films |                                |                       |  | Left ventricular excursion |
|--------------------|----------------|--------|------------------------|--------------|----------------------------------|--------------------|---------------------------|------------------------------------|---------------------------|-------------------------|---------------------------|--------------|------------------------------|--------------------------------|-----------------------|--|----------------------------|
|                    |                |        | Arterial               | Mixed venous |                                  |                    |                           |                                    |                           |                         | Arterial                  | Mixed venous | Heart area                   | Heart area per cent of initial | Change in heart area* | Rib, or intercostal space photographed |                            |
|                    |                |        |                        |              | volumes per cent                 | volumes per cent   | volumes per cent          | cc per minute                      | cc                        | per cent                |                           |              |                              |                                |                       |  |                            |
| 162 Female         | May 23, 1927   | 17 1   | 18 84                  | 16 73        | 2 11                             | 106                | 5,024                     | 100 0                              |                           | 19 80                   | 94 1                      | 82           | 60 8                         | 100 0                          |                       |  |                            |
|                    | May 24, 1927   |        | 21 97                  | 17 00        | 4 97                             | 106                | 2,133                     | 42 0                               | -58 0                     | 22 00                   | 98 9                      | 78           | 49 0                         | 74 4                           | -25 6                 |  |                            |
|                    | May 25, 1927   |        | 19 04                  | 16 42        | 2 62                             | 111                | 4,237                     | 84 0                               | -16 0                     | 20 03                   | 94 1                      | 81           | 61 6                         | 93 6                           | -6 4                  |  |                            |
|                    | May 27, 1927   |        | 18 86                  | 15 10        | 3 76                             | 122                | 3,249                     | 64 0                               | -36 0                     | 19 78                   | 94 3                      | 77           | 55 5                         | 84 3                           | -15 1                 |  |                            |
|                    | June 1, 1927   |        | 16 53                  | 13 86        | 2 67                             | 119                | 4,459                     | 89 0                               | -11 0                     | 16 80                   | 97 2                      | 82           | 62 4                         | 94 9                           | -5 1                  |  |                            |
|                    |                |        | 13 75                  | 11 96        | 1 74                             | 124                | 7,084                     | 120 0                              | +20 0                     | 14 91                   | 98 5                      | 86           | 60 4                         | 100 0                          |                       |  |                            |
|                    | March 19, 1928 | 17 4   | 15 51                  | 13 77        | 1 74                             | 116                | 6,663                     | 100 0                              |                           | 16 04                   | 95 5                      | 8            | 18 5                         | 100 0                          |                       |  |                            |
|                    | March 20, 1928 | 16 5   | 18 43                  | 13 46        | 4 97                             | 109                | 2,163                     | 32 9                               | -67 1                     | 20 02                   | 91 1                      | 66           | 67 1                         | 19 8                           | -20 2                 |  |                            |
|                    | March 21, 1928 | 15 9   | 17 31                  | 13 55        | 3 76                             | 109                | 2,900                     | 43 5                               | -56 5                     | 18 50                   | 92 5                      | 17           | 70 1                         | 90 1                           | -9 9                  |  |                            |
|                    |                |        | 15 70                  | 11 79        | 3 91                             | 106                | 2,710                     | 41 3                               | -58 7                     | 16 45                   | 94 2                      | 71           | 71 2                         | 90 7                           | -9 3                  |  |                            |
|                    | March 29, 1928 | 14 5   | 14 05                  | 10 08        | 3 97                             | 98                 | 2,468                     | 100 0                              |                           | 14 98                   | 92 4                      | 6            | 70 2                         | 100 0                          |                       | 6th rib                                | 2 1                        |
|                    | March 30, 1928 | 13 5   | 15 42                  | 9 69         | 5 73                             | 95                 | 1,657                     | 67 2                               | -32 8                     | 16 48                   | 92 3                      | 5            | 51 3                         | 81 6                           | -18 4                 | 6th rib                                | 3 1                        |
| April 2, 1928      | 13 6           | 14 27  | 10 08                  | 4 19         | 96                               | 2,292              | 92 9                      | -7 1                               | 15 65                     | 90 0                    | 6                         | 60 6         | 86 4                         | -13 6                          | 6th rib               | 3 8                                    |                            |
| 161 Male           | June 6, 1927   | 14 8   | 12 76                  | 8 86         | 3 90                             | 98                 | 2,538                     | 102 7                              | +2 7                      | 13 99                   | 89 8                      | 6            | 63 8                         | 90 9                           | -9 1                  | 6th rib                                | 3 4                        |
|                    | June 7, 1927   |        | 17 11                  | 15 34        | 1 77                             | 154                | 8,700                     | 100 0                              |                           | 17 94                   | 94 2                      | 5            | 11 4                         | 100 0                          |                       |  |                            |
|                    | June 8, 1927   |        | 18 86                  | 14 58        | 4 28                             | 144                | 3,365                     | 38 0                               | -62 0                     | 19 82                   | 94 1                      | 1            | 51 6                         | 80 1                           | -19 3                 |  |                            |
|                    | June 10, 1927  |        | 18 82                  | 15 08        | 3 74                             | 148                | 3,959                     | 45 0                               | -55 0                     | 19 20                   | 96 9                      | 1            | 61 3                         | 86 1                           | -13 9                 |  |                            |
|                    | June 10, 1927  |        | 17 36                  | 12 99        | 4 37                             | 138                | 3,159                     | 36 0                               | -64 0                     | 18 10                   | 94 8                      | 1            | 59 9                         | 83 8                           | -16 2                 |  |                            |

\* In this column, + indicates increase, and - decrease

† Before calculating the oxygen saturations 0.2 and 0.1 volume per cent (the amount of oxygen in per cent solution) were subtracted from the arterial and mixed venous oxygen contents respectively

§ Tincture of digitalis unless otherwise indicated

|| N R = normal rhythm, A.F = auricular fibrillation, V P C = ventricular premature contraction

A P C = auricular premature contractions, Vent. Par Tach = ventricular paroxysmal tachycardia, I-H = incomplete heart block, + P-R = conduction time increased

† The x ray photographs from which others at a distance of 34 inches

1.0 cc. of this was given

\*\* 2.5 cc. of this was given sub

TABLE 2

| Dog number and sex   | Date           | Weight | O <sub>2</sub> content |                  | Arterio venous oxygen difference | Oxygen consumption | Cardiac output per minute | Cardiac output per cent of initial | Change in cardiac output* | O <sub>2</sub> capacity | O <sub>2</sub> saturation |              |
|----------------------|----------------|--------|------------------------|------------------|----------------------------------|--------------------|---------------------------|------------------------------------|---------------------------|-------------------------|---------------------------|--------------|
|                      |                |        | Arterial               | Mixed venous     |                                  |                    |                           |                                    |                           |                         | Arterial                  | Mixed venous |
|                      |                | kgm    | volumes per cent       | volumes per cent | volumes per cent                 | cc per minute      | cc                        | per cent                           | per cent                  | vol-umes per cent       | per cent                  | per cent     |
| 161 Male (continued) | March 27, 1928 | 13 9   | 17 67                  | 15 10            | 2 57                             | 104                | 4,048                     | 100 0                              |                           | 18 95                   | 92 2                      | 79           |
|                      | March 28, 1928 | 13 0   | 19 91                  | 15 96            | 3 95                             | 109                | 2,760                     | 68 2                               | -31 8                     | 21 70                   | 90 9                      | 73           |
|                      | March 31, 1928 | 13 0   | 20 59                  | 14 15            | 6 44                             | 105                | 1,630                     | 40 3                               | -59 7                     | 22 40                   | 91 0                      | 62           |
|                      | March 31, 1928 | 13 0   | 17 64                  | 12 97            | 4 67                             | 108                | 2,313                     | 57 2                               | -42 8                     | 18 55                   | 94 0                      | 69           |
| 158 Male             | May 31, 1927   | 20 2   | 20 32                  | 19 04            | 1 28                             | 128                | 10,000                    | 100 0                              |                           | 21 17                   | 95 0                      | 89           |
|                      |                |        | 19 08                  | 14 00            | 5 08                             | 126                | 2,480                     | 25 0                               | -75 0                     | 19 85                   | 95 8                      | 70           |
|                      | June 1, 1927   |        | 20 34                  | 16 80            | 3 52                             | 136                | 3,841                     | 38 0                               | -62 0                     | 21 59                   | 94 2                      | 77           |
|                      | June 2, 1927   |        | 18 77                  | 16 73            | 2 04                             | 142                | 6,960                     | 70 0                               | -30 0                     | 19 67                   | 94 4                      | 84           |
|                      | June 9, 1927   | 19 2   | 16 91                  | 15 39            | 1 52                             | 130                | 8,553                     | 100 0                              |                           | 17 45                   | 95 7                      | 87           |
|                      |                |        | 20 41                  | 15 37            | 5 04                             | 131                | 2,600                     | 35 0                               | -65 0                     | 21 64                   | 93 3                      | 70           |
|                      | June 10, 1927  |        | 19 44                  | 14 58            | 4 86                             | 111                | 2,284                     | 27 0                               | -73 0                     | 21 21                   | 90 7                      | 68           |
|                      | June 11, 1927  |        | 16 66                  | 13 73            | 2 93                             | 112                | 3,823                     | 45 0                               | -55 0                     | 18 08                   | 91 0                      | 75           |
|                      | March 22, 1928 | 20 3   | 20 60                  | 18 66            | 1 94                             | 126                | 6,500                     | 100 0                              |                           | 21 38                   | 95 5                      | 86           |
|                      |                |        | 22 78                  | 19 30            | 3 48                             | 119                | 3,418                     | 52 6                               | -47 4                     | 24 47                   | 92 3                      | 78           |
|                      | March 23, 1928 | 18 3   | 23 20                  | 17 90            | 5 30                             | 126                | 2,370                     | 36 5                               | -63 5                     | 24 07                   | 95 6                      | 74           |
|                      | March 24, 1928 | 17 9   | 21 27                  | 18 34            | 2 93                             | 132                | 4,510                     | 69 4                               | -30 6                     | 22 88                   | 92 1                      | 79           |
|                      | March 26, 1928 | 18 5   | 19 02                  | 14 86            | 4 16                             | 123                | 2,960                     | 45 6                               | -55 4                     | 20 37                   | 92 4                      | 72           |

TABLE 1

| Dog number<br>and sex           | Date           | Weight | O <sub>2</sub> content |                     | Arterio venous oxygen difference | Oxygen consumption      | Cardiac output per minute | Cardiac output per cent of initial | Change in cardiac output* | O <sub>2</sub> capacity | O <sub>2</sub> saturation |          |
|---------------------------------|----------------|--------|------------------------|---------------------|----------------------------------|-------------------------|---------------------------|------------------------------------|---------------------------|-------------------------|---------------------------|----------|
|                                 |                |        | Arterial               | Mixed venous        |                                  |                         |                           |                                    |                           |                         | Arterial                  | Arterial |
|                                 |                | kgm    | volumes<br>per cent    | volumes<br>per cent | volumes<br>per cent              | cc<br>per<br>min<br>ute | cc                        | per cent                           | per cent                  | volumes<br>per<br>cent  | per<br>cent               | per cent |
| 161<br>Male<br>(con-<br>tinued) | March 27, 1928 | 13 9   | 17 67                  | 15 10               | 2 57                             | 104                     | 4,048                     | 100 0                              |                           | 18 95                   | 92 2                      | 7        |
|                                 | March 28, 1928 | 13 0   | 19 91                  | 15 96               | 3 95                             | 109                     | 2,760                     | 68 2                               | -31 8                     | 21 70                   | 90 9                      | 7        |
|                                 | March 31, 1928 | 13 0   | 20 59                  | 14 15               | 6 44                             | 105                     | 1,630                     | 40 3                               | -59 7                     | 22 40                   | 91 0                      | 6        |
|                                 | March 31, 1928 | 13 0   | 17 64                  | 12 97               | 4 67                             | 108                     | 2,313                     | 57 2                               | -42 8                     | 18 55                   | 94 0                      | 6        |
| 158<br>Male                     | May 31, 1927   | 20 2   | 20 32                  | 19 04               | 1 28                             | 128                     | 10,000                    | 100 0                              |                           | 21 17                   | 95 0                      | 8        |
|                                 | June 1, 1927   |        | 19 08                  | 14 00               | 5 08                             | 126                     | 2,480                     | 25 0                               | -75 0                     | 19 85                   | 95 8                      | 70       |
|                                 | June 2, 1927   |        | 20 34                  | 16 80               | 3 52                             | 136                     | 3,841                     | 38 0                               | -62 0                     | 21 59                   | 94 2                      | 71       |
|                                 | June 2, 1927   |        | 18 77                  | 16 73               | 2 04                             | 142                     | 6,960                     | 70 0                               | -30 0                     | 19 67                   | 94 4                      | 84       |
|                                 | June 9, 1927   | 19 2   | 16 91                  | 15 39               | 1 52                             | 130                     | 8,553                     | 100 0                              |                           | 17 45                   | 95 7                      | 87       |
|                                 |                |        | 20 41                  | 15 37               | 5 04                             | 131                     | 2,600                     | 35 0                               | -65 0                     | 21 64                   | 93 3                      | 70       |
|                                 | June 10, 1927  |        | 19 44                  | 14 58               | 4 86                             | 111                     | 2,284                     | 27 0                               | -73 0                     | 21 21                   | 90 7                      | 68       |
|                                 | June 11, 1927  |        | 16 66                  | 13 73               | 2 93                             | 112                     | 3,823                     | 45 0                               | -55 0                     | 18 08                   | 91 0                      | 75       |
|                                 | March 22, 1928 | 20 3   | 20 60                  | 18 66               | 1 94                             | 126                     | 6,500                     | 100 0                              |                           | 21 38                   | 95 5                      | 86       |
|                                 | March 23, 1928 | 18 3   | 22 78                  | 19 30               | 3 48                             | 119                     | 3,418                     | 52 6                               | -47 4                     | 24 47                   | 92 3                      | 78       |
|                                 | March 24, 1928 | 17 9   | 23 20                  | 17 90               | 5 30                             | 126                     | 2,370                     | 36 5                               | -63 5                     | 24 07                   | 95 6                      | 74       |
|                                 | March 26, 1928 | 18 5   | 21 27                  | 18 34               | 2 93                             | 132                     | 4,510                     | 69 4                               | -30 6                     | 22 88                   | 92 1                      | 79       |
|                                 | March 26, 1928 | 18 5   | 19 02                  | 14 86               | 4 16                             | 123                     | 2,960                     | 45 6                               | -55 4                     | 20 37                   | 92 4                      | 72       |



TABLE 2

| Dog number<br>and sex | Date           | Weight | O <sub>2</sub> content |                     | Arterio-venous oxygen difference | Oxygen consumption       | Cardiac output per minute | Cardiac output per cent of initial | Change in cardiac output* | O <sub>2</sub> capacity     | O <sub>2</sub> saturation |              |
|-----------------------|----------------|--------|------------------------|---------------------|----------------------------------|--------------------------|---------------------------|------------------------------------|---------------------------|-----------------------------|---------------------------|--------------|
|                       |                |        | Arterial               | Mixed venous        |                                  |                          |                           |                                    |                           |                             | Arterial                  | Mixed venous |
|                       |                | kgm    | volumes<br>per cent    | volumes<br>per cent | volumes<br>per cent              | cc<br>per<br>min-<br>ute | cc                        | per cent                           | per cent                  | vol-<br>umes<br>per<br>cent | per<br>cent               | per<br>cent  |
| 155<br>Female         | May 16, 1927   | 31 9   | 20 18                  | 17 60               | 2 58                             | 161                      | 6,240                     | 100 0                              |                           | 21 95                       | 91 0                      | 80 0         |
|                       |                |        | 20 78                  | 16 75               | 4 05                             | 143                      | 3,531                     | 56 0                               | -44 0                     | 21 24                       | 92 5                      | 74 8         |
|                       | May 17, 1927   |        | 20 58                  | 17 56               | 3 02                             | 173                      | 5,728                     | 92 0                               | -8 0                      | 21 28                       | 95 8                      | 82 5         |
|                       | May 18, 1927   |        | 19 69                  | 17 16               | 2 53                             | 154                      | 6,088                     | 98 0                               | -2 0                      | 20 36                       | 95 7                      | 83 9         |
|                       | May 19, 1927   |        | 18 77                  | 16 13               | 2 64                             | 155                      | 5,871                     | 94 0                               | -6 0                      | 19 24                       | 96 5                      | 83 3         |
| 171<br>Female         | June 7, 1927   | 16 4   | 20 85                  | 19 10               | 1 75                             | 158                      | 9,028                     | 100 0                              |                           | 21 73                       | 95 0                      | 87 3         |
|                       |                |        | 23 43                  | 12 92               | 10 51                            | 162                      | 1,541                     | 17 0                               | -83 0                     | 24 35                       | 95 4                      | 52 7         |
|                       | June 8, 1927   |        | 25 00                  | 11 76               | 13 24                            | 173                      | 1,307                     | 14 0                               | -86 0                     | 26 30                       | 94 3                      | 43 0         |
|                       | June 9, 1927   |        |                        |                     |                                  |                          |                           |                                    |                           |                             |                           |              |
| 90<br>Male            | March 26, 1928 | 10 6   | 19 48                  | 16 22               | 3 26                             | 59                       | 1,810                     | 100 0                              |                           | 20 31                       | 95 0                      | 79 4         |
|                       |                |        | 22 22                  | 17 99               | 4 23                             | 59                       | 1,395                     | 77 0                               | -23 0                     | 23 17                       | 95 1                      | 77 2         |
|                       | March 27, 1928 | 9 9    | 20 66                  | 8 57                | 12 09                            | 59                       | 488                       | 27 0                               | -73 0                     | 23 02                       | 92 9                      | 38 5         |

TABLE 2

| Dog number<br>and sex | Date           | Weight | O <sub>2</sub> content |                     | Arterio-venous oxygen difference | Oxygen consumption      | Cardiac output per minute | Cardiac output per cent of initial | Change in cardiac output* | O <sub>2</sub> capacity | O <sub>2</sub> saturation† |              |
|-----------------------|----------------|--------|------------------------|---------------------|----------------------------------|-------------------------|---------------------------|------------------------------------|---------------------------|-------------------------|----------------------------|--------------|
|                       |                |        | Arterial               | Mixed venous        |                                  |                         |                           |                                    |                           |                         | Arterial                   | Mixed venous |
|                       |                | kgm    | volumes<br>per cent    | volumes<br>per cent | volumes<br>per cent              | cc<br>per<br>min<br>ute | cc                        | per cent                           | per cent                  | volumes<br>per cent     | per cent                   | per cent     |
| 155<br>Female         | May 16, 1927   | 31 9   | 20 18                  | 17 60               | 2 58                             | 161                     | 6,240                     | 100 0                              |                           | 21 95                   | 91 0                       | 80 0         |
|                       |                |        | 20 78                  | 16 75               | 4 05                             | 143                     | 3,531                     | 56 0                               | -44 0                     | 21 24                   | 92 5                       | 74 8         |
|                       | May 17, 1927   |        | 20 58                  | 17 56               | 3 02                             | 173                     | 5,728                     | 92 0                               | -8 0                      | 21 28                   | 95 8                       | 82 1         |
|                       | May 18, 1927   |        | 19 69                  | 17 16               | 2 53                             | 154                     | 6,088                     | 98 0                               | -2 0                      | 20 36                   | 95 7                       | 83 9         |
|                       | May 19, 1927   |        | 18 77                  | 16 13               | 2 64                             | 155                     | 5,871                     | 94 0                               | -6 0                      | 19 24                   | 96 5                       | 83 3         |
| 171<br>Female         | June 7, 1927   | 16 4   | 20 85                  | 19 10               | 1 75                             | 158                     | 9,028                     | 100 0                              |                           | 21 73                   | 95 0                       | 87 5         |
|                       |                |        | 23 43                  | 12 92               | 10 51                            | 162                     | 1,541                     | 17 0                               | -83 0                     | 24 35                   | 95 4                       | 52 7         |
|                       | June 8, 1927   |        | 25 00                  | 11 76               | 13 24                            | 173                     | 1,307                     | 14 0                               | -86 0                     | 26 30                   | 94 3                       | 43 6         |
|                       | June 9, 1927   |        |                        |                     |                                  |                         |                           |                                    |                           |                         |                            |              |
| 90<br>Male            | March 26, 1928 | 10 6   | 19 48                  | 16 22               | 3 26                             | 59                      | 1,810                     | 100 0                              |                           | 20 31                   | 95 0                       | 79 4         |
|                       |                |        | 22 22                  | 17 99               | 4 23                             | 59                      | 1,395                     | 77 0                               | -23 0                     | 23 17                   | 95 1                       | 77 2         |
|                       | March 27, 1928 | 9 9    | 20 66                  | 8 57                | 12 09                            | 59                      | 488                       | 27 0                               | -73 0                     | 23 02                   | 92 9                       | 38 5         |

## OBSERVATIONS

*Effect of digitalis on cardiac output* Mitral insufficiency was created in dog 162 on January 13, 1925,  $2\frac{1}{2}$  years ago. The heart area increased 20 per cent during this time, from 55.0 to 65.8 sq cm (table 1). The cardiac output on May 23, 1927, was 5024 cc per minute (table 2). Two hours after injection of tincture of digitalis 3.5 cc, the output decreased to 2133 cc per minute, 23 hours after, it increased to 4237 cc, 45 hours after it fell to 3249 cc,  $81\frac{1}{2}$  hours after it was 4459 cc, and  $103\frac{1}{2}$  hours after, 7084 cc. The decrease (58 per cent) in cardiac output was at a maximum 2 hours after digitalis was given. The output returned to normal with slight fluctuations toward the end of the 8th day.

On March 19, 1928, the experiment was repeated  $3\frac{1}{6}$  years after the first operation. The heart had enlarged 22 per cent (table 1). The cardiac output was 6663 cc per minute (table 2). Tincture of digitalis 4.0 cc was then administered intravenously. Three hours later the output fell to 2193 cc but increased the following day to 2900 cc. The output had not returned to normal 9 days later and was only 2468 cc per minute. On March 29, tincture of digitalis 2.3 cc was again injected intravenously, and was followed by a fall in cardiac output to 1657 cc or 67.2 per cent of the initial measurement, in 3 hours (table 2, fig. 1). At the end of four days the cardiac output returned to 2535 cc or 102.7 per cent of the output at the beginning of this period (March 29, 1928). On three occasions accordingly the administration of digitalis in this dog was followed by decreases in cardiac output.

Mitral insufficiency was created in dog 161 in December 11, 1924,  $2\frac{1}{2}$  years ago. During this time the area of the heart increased 55 per cent from 46.0 to 71.4 sq cm (table 1). The cardiac output was estimated on June 6, 1927, and found to be 8700 cc per minute (table 2). Tincture of digitalis 3.3 cc was then given intravenously. When estimated 2 hours later the output was found to have decreased to 3365 cc per minute. The measurement 21 hours after injection rose to 3959 cc, but after 48 hours it again fell to 3159 cc, after 96 hours it increased to 7514 cc. There was accordingly a decrease of 62 per cent in cardiac output immediately after giving digitalis. At the end of four days the effect had nearly worn off.

## OBSERVATIONS

*Effect of digitalis on cardiac output* Mitral insufficiency was created in dog 162 on January 13, 1925,  $2\frac{1}{2}$  years ago. The heart area increased 20 per cent during this time, from 55.0 to 65.8 sq cm (table 1). The cardiac output on May 23, 1927, was 5024 cc per minute (table 2). Two hours after injection of tincture of digitalis 3.5 cc, the output decreased to 2133 cc per minute, 23 hours after, it increased to 4237 cc, 45 hours after it fell to 3249 cc,  $81\frac{1}{2}$  hours after it was 4459 cc, and  $103\frac{1}{2}$  hours after, 7084 cc. The decrease (58 per cent) in cardiac output was at a maximum 2 hours after digitalis was given. The output returned to normal with slight fluctuations toward the end of the 8th day.

On March 19, 1928, the experiment was repeated  $3\frac{1}{6}$  years after the first operation. The heart had enlarged 22 per cent (table 1). The cardiac output was 6663 cc per minute (table 2). Tincture of digitalis 4.0 cc was then administered intravenously. Three hours later the output fell to 2193 cc but increased the following day to 2900 cc. The output had not returned to normal 9 days later and was only 2468 cc per minute. On March 29, tincture of digitalis 2.3 cc was again injected intravenously, and was followed by a fall in cardiac output to 1657 cc or 67.2 per cent of the initial measurement, in 3 hours (table 2, fig. 1). At the end of four days the cardiac output returned to 2535 cc or 102.7 per cent of the output at the beginning of this period (March 29, 1928). On three occasions accordingly the administration of digitalis in this dog was followed by decreases in cardiac output.

Mitral insufficiency was created in dog 161 in December 11, 1924,  $2\frac{1}{2}$  years ago. During this time the area of the heart increased 55 per cent from 46.0 to 71.4 sq cm (table 1). The cardiac output was estimated on June 6, 1927, and found to be 8700 cc per minute (table 2). Tincture of digitalis 3.3 cc was then given intravenously. When estimated 2 hours later the output was found to have decreased to 3365 cc per minute. The measurement 21 hours after injection rose to 3959 cc, but after 48 hours it again fell to 3159 cc, after 96 hours it increased to 7514 cc. There was accordingly a decrease of 62 per cent in cardiac output immediately after giving digitalis. At the end of four days the effect had nearly worn off.

The experiment was repeated 9 months later on March 27, 1928. It was now  $3\frac{1}{4}$  years since operation. The heart had increased in size 77 per cent (table 1). The cardiac output was 4048 cc per minute (table 2). Tincture of digitalis 2.6 cc was given intravenously and 0.5 cc subcutaneously. The output fell 3 hours later to 2760 cc and 24 hours later still further, to 1630 cc. It rose to 2313 cc 4 days after injection. There was then a maximum fall of 60 per cent in cardiac output followed by return toward normal.

Mitral insufficiency was created in dog 158 on December 2, 1924,  $2\frac{1}{2}$  years ago. The area of the heart increased (82 per cent) from 46.4 to 84.3 sq cm (table 1). The cardiac output on May 31, 1927 was 10,000 cc per minute (table 2). Two hours after the injection of tincture of digitalis 4.6 cc the output fell to 2480 cc, 20 hours after, it rose to 3841 cc, and 45 hours after, it rose further to 6960 cc. A week later it rose still further to 8553 cc, nearly to the level existing before digitalis was administered. On June 6, 1927, tincture of digitalis 4.4 cc was given again. Two hours later the output decreased to 2600 cc per minute, and 24 hours afterward decreased further to 2284 cc. At the end of 47 hours the cardiac output began to increase and was found to be 3823 cc. The output decreased then 75 per cent following the administration of digitalis and slowly returned toward normal.

Digitalis was given again 10 months later. Mitral insufficiency had now been established for  $3\frac{1}{3}$  years. During this time the heart area increased 94 per cent from 46.4 sq cm to 90.2 sq cm (table 1). The cardiac output on March 22, 1928 was 6500 cc per minute (table 2). Tincture of digitalis 4.3 cc was injected intravenously. The output fell 3 hours later to 3418 cc, 1 day later it fell further to 2370 cc, 1 day later still it increased to 4510 cc and 2 days later, that is to say, 4 days after injection it fell again to 2960 cc. There was a maximum decrease (64 per cent) in cardiac output 25 hours after the injection of digitalis, followed by a slow return toward normal. On three occasions the same result followed the administration of digitalis, there was always a decrease in cardiac output.

Mitral insufficiency was created in dog 155 on February 25, 1925,  $2\frac{1}{2}$  years ago. After this the dog became pregnant and was delivered of 5 puppies without developing any signs of heart failure. The area

The experiment was repeated 9 months later on March 27, 1928. It was now  $3\frac{1}{4}$  years since operation. The heart had increased in size 77 per cent (table 1). The cardiac output was 4048 cc per minute (table 2). Tincture of digitalis 2.6 cc was given intravenously and 0.5 cc subcutaneously. The output fell 3 hours later to 2760 cc and 24 hours later still further, to 1630 cc. It rose to 2313 cc 4 days after injection. There was then a maximum fall of 60 per cent in cardiac output followed by return toward normal.

Mitral insufficiency was created in dog 158 on December 2, 1924,  $2\frac{1}{2}$  years ago. The area of the heart increased (82 per cent) from 46.4 to 84.3 sq cm (table 1). The cardiac output on May 31, 1927 was 10,000 cc per minute (table 2). Two hours after the injection of tincture of digitalis 4.6 cc the output fell to 2480 cc, 20 hours after, it rose to 3841 cc, and 45 hours after, it rose further to 6960 cc. A week later it rose still further to 8553 cc, nearly to the level existing before digitalis was administered. On June 6, 1927, tincture of digitalis 4.4 cc was given again. Two hours later the output decreased to 2600 cc per minute, and 24 hours afterward decreased further to 2284 cc. At the end of 47 hours the cardiac output began to increase and was found to be 3823 cc. The output decreased then 75 per cent following the administration of digitalis and slowly returned toward normal.

Digitalis was given again 10 months later. Mitral insufficiency had now been established for  $3\frac{1}{3}$  years. During this time the heart area increased 94 per cent from 46.4 sq cm to 90.2 sq cm (table 1). The cardiac output on March 22, 1928 was 6500 cc per minute (table 2). Tincture of digitalis 4.3 cc was injected intravenously. The output fell 3 hours later to 3418 cc, 1 day later it fell further to 2370 cc, 1 day later still it increased to 4510 cc and 2 days later, that is to say, 4 days after injection it fell again to 2960 cc. There was a maximum decrease (64 per cent) in cardiac output 25 hours after the injection of digitalis, followed by a slow return toward normal. On three occasions the same result followed the administration of digitalis, there was always a decrease in cardiac output.

Mitral insufficiency was created in dog 155 on February 25, 1925,  $2\frac{1}{3}$  years ago. After this the dog became pregnant and was delivered of 5 puppies without developing any signs of heart failure. The area

as an example On March 19, 1928, the area of the heart was 78.5 sq cm (table 2) Digitalis was then administered and three hours later the area diminished to 62.7 sq cm, 79.8 per cent of the initial value. There was an increase 2 days later to 71.2 sq cm or 90.7 per cent of the first measurement. Ten days later, on March 29, 1928, digitalis was again injected. The area of the heart at this time was 70.2 sq cm (table 2, figs 1 and 3). Three hours afterward the area decreased to 57.3 sq cm or 81.6 per cent of the size before this injection. The area increased slightly to 60.6 sq cm 24 hours later, or 86.4 per cent. The size 4 days later increased still more to 63.8 sq cm or 90.9 per cent. On both occasions the size of the heart decreased within 24 hours, 20 and 18 per cent respectively. Then it gradually increased as the effect of digitalis wore off. This dog had been given digitalis 9 months before (table 2) and on this occasion also there was a decrease in size of 25.6 per cent.

The effect of digitalis in the other dogs was similar to that just described. Digitalis was given to dog 161 on two occasions (table 2), to dog 171 once (table 2), to dog 155 once (table 2), to dog 158 on three occasions (table 2) and to dog 90 once (table 2, fig 2). The greatest decrease detected occurred sometimes at  $2\frac{1}{2}$  hours and at other times 24 hours after the injection of digitalis and varied in extent between 11 and 29 per cent. Decrease was followed by increase in size as the effect of digitalis diminished.

*Effect of digitalis on ventricular contraction of enlarged hearts* On March 29, 1928 in dog 162 the *left* ventricular excursion was 2.1 mm at the level of the 6th rib (table 2, figs 1 and 4). Digitalis was then given. The *left* ventricular excursion 3 hours later was 3.7 mm. At the end of the first day it was 3.8 mm, and at the end of the fourth, it was 3.4 mm. The *right* ventricular excursion increased from 3.6 mm to a maximum of 7.3 mm. The maximum increase of the left ventricular excursion was accordingly 181 per cent and of the right 200 per cent. As the effect of digitalis wore off the excursions became small.

There are observations like these in 3 other dogs (table 2, fig 2). All behaved alike. The increase in height of excursion of the left ventricle ranged between 16 and 81 per cent. Whenever right ventricular excursions could be measured, increases attaining 100 per cent were observed. In all cases, measurement was however not possible.

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TABLE 3

*Summary of effect of digitalis on the electrocardiograms of dogs with enlarged hearts*

| Dog number | Date           | Ventricular rate | P R interval | T waves | Abnormalities due to digitalis | Degree of enlargement of heart |
|------------|----------------|------------------|--------------|---------|--------------------------------|--------------------------------|
|            |                |                  |              |         |                                | <i>per cent</i>                |
| 90         | March 26, 1928 | 0                | 0            | c       | Vent Par Tach.                 | 5                              |
| 158        | May 31, 1927   | —                | +            | c       | A P C                          | 82                             |
|            | June 9, 1927   | +                | +            | c       | Vent. Par Tach                 | 82                             |
|            | March 22, 1928 | +                | +            | c       | Aur Fib, V P C                 | 94                             |
| 155        | May 16, 1927   | —                | +            | c       | None                           | 18                             |
| 161        | June 6, 1927   | —                | 0            | c       | None                           | 55                             |
|            | March 27, 1928 | +                | 0            | c       | Runs of Vent Par Tach.         | 77                             |
| 162        | May 23, 1927   | 0                | 0            | c       | V P C                          | 20                             |
|            | March 19, 1928 | 0                | +            | c       | I-H B                          | 22                             |
|            | March 29, 1928 | 0                | 0            | c       | None                           | 22                             |
| 171        | June 7, 1927   | +                | 0            | c       | None                           | 24                             |

c = changed, 0 = unchanged, + = increased, — = decreased Vent Par Tach = Ventricular paroxysmal tachycardia A P C = Auricular premature contractions Aur fib = Auricular fibrillation V P C = Ventricular premature contractions I-H B = Incomplete heart block

FIG 4 In this figure are reproduced photographs of the moving films obtained in the manner described in the preceding paper (Cohn and Stewart, 1928) Below each photograph are placed tracings of the original films which show the excursions made by the right and left ventricles respectively When these photographs were taken the time marker was not working properly The film was moving however, at a constant speed The photographs are reduced to one-fourth of their natural size

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|            | March 29, 1928 | 0                | 0            | c       | None                           | 22                             |
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dogs (dogs 155, 158 and 162) Evidence of toxic action was manifested in the form of irregularity in all dogs except 155 and 171 Paroxysmal ventricular tachycardia was encountered in 3 dogs (dogs 90, 158 and 161) Auricular premature contractions were observed once (dog 158), ventricular premature contractions (without paroxysmal ventricular tachycardia) twice (dogs 158 and 162), incomplete heart block once (dog 162) and auricular fibrillation once (dog 158) These effects were all transient and occurred at the height of the action of digitalis

#### DISCUSSION

In the light of these experiments it appears that the effect of giving digitalis results just as was the case in normal dogs in decreasing the cardiac output and the size of the heart and in increasing the height of ventricular excursions in dogs in which the hearts are enlarged but in which the signs of heart failure have not developed Whether enlargement was due to dilatation or to hypertrophy or to both we do not know, for most of the animals are still alive There can be no doubt however that at the time of observation they were in a state of compensation, for they ran on a treadmill as long and with as great ease as did normal dogs

As in normal dogs, giving digitalis increased the tone of heart muscle, an effect which is reflected in the decreased size of the heart The cardiac output was in consequence also decreased Again as in normal dogs contraction increased, the result of which tended to increase cardiac output And finally, the effect on cardiac output which depends upon the net result of the interaction of these two functions varied For the first 24 hours the effect on tone overbalanced that on contraction so that cardiac output was uniformly decreased But when the action of digitalis began to diminish, the rate at which it did so, differed in the various functions, so that the effect on contraction measured in terms of the height of the ventricular excursions exceeded the effect on tone, estimated in terms of the size of the heart, or persisted long after the effect upon it (tone) began to diminish In such instances, the cardiac output returned to normal or overshot this mark, due to the increased extent of ventricular excursion, even though the heart sometimes continued to be smaller than it had been in the beginning (dog 162, (table 2 and fig 1)

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two curves We believe we are correct in referring the irregularities to the influence of ventricular contraction Where the peaks occur, increase in the height of excursion was great enough to effect cardiac output, increase in excursion then overbalanced decrease in size and permitted an excess in output beyond that which would have been anticipated from the slope of the curve All of this, as well as the origin of the blood responsible for the unlooked for results are discussed also in the preceding paper

Two dogs (dogs 90 and 171, table 2) died following the administration of digitalis The cardiac size was decreased in them as much as 25 per cent below the original measurement and the cardiac output 73 and 86 per cent respectively Whether death was due to the inability of the small heart to pump enough blood to maintain life, or whether it was due to a toxic effect on the heart muscle we do not know Paroxysmal ventricular tachycardia occurred in dog 90, but the normal rhythm continued to be present in dog 171 (table 2)

The changes in the electrocardiograms were on the whole more pronounced in these dogs than in the normal ones An effect was found constantly in form of the T-waves (tables 2 and 3) Auriculo-ventricular conduction time increased in 3 dogs (dogs 155, 158 and 162) and on each of the 3 occasions on which digitalis was given to dog 158 (table 3) Abnormal rhythms (paroxysmal ventricular tachycardia, auricular fibrillation and incomplete heart block) as well as ectopic beats of auricular and ventricular origin were encountered They were found perhaps more frequently in this group than in the normal dogs That abnormal mechanisms are expected when digitalis is prescribed in large hearts oftener and rather than in normal ones is a consequence of clinical experience But whether their occurrence is a result of size merely or whether both size and irregularity of action are dependent on a common underlying fault is not yet, so far as we know, understood

The fact has been mentioned that dog 90 did not show cardiac enlargement (table 1) At the time of operation a soft systolic murmur appeared at the mitral area and persisted for several months Then it disappeared leaving only a sharp first sound Since cardiac enlargement did not develop in the absence of the murmur it is probable that no lesion of sufficient extent resulted from the operation

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Regen (1927) showed. Though the heart does not become smaller, an influence on its size may nevertheless be demonstrated, as was shown by Levy (1923) in the case of lobar pneumonia. In this disease enlargement of the heart did not take place, or at least tended to occur less frequently if this drug was given. We have ourselves shown that in patients increase in ventricular excursions may take place after digitalis administration (Cohn and Stewart, 1924), even though no demonstrable change in the size of the heart can be seen in x-ray photographs. If there is increase in contraction and no decrease in size of the heart the experiments which are now reported permit the inference that cardiac output increases. This may be the situation in heart failure in man, but of this there is no direct evidence. Should the mechanism of heart failure involve decrease in the volume output, as has until recently been generally believed to be the case, point would be given to what Starling (1918) described as the law of the heart. Starling believed, and showed in experiments, that when heart muscle fibers increased beyond a certain optimal length, decrease in output from the heart resulted. If the optimal, or a somewhat shorter length, were restored, output from the ventricles mounted. Heart failure may be a condition in which the fibers are longer than optimal, were digitalis able to restore them to a proper length, the requirement of the situation would be met. We have no information that contributes to an elucidation of this problem, but these considerations may explain why in the absence of heart failure, that is to say of edema, the results in our dogs so far as alterations in volume output are concerned are without specific value. The condition in them is simply not that of heart failure, they cannot be expected therefore to illustrate the mechanism which obtains in that condition.

#### SUMMARY

We have studied the effect of digitalis upon the cardiac output, cardiac size and ventricular contraction of dogs with enlarged hearts, but without signs of heart failure. We have found in them, as in normal dogs, that

- 1 The size of the heart is decreased
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the mean pulmonary blood velocity<sup>2</sup> According to the formula of G N Stewart (3),  $Q$  equals  $\frac{VT}{60}$  where  $Q$  is the quantity of blood in the lungs,  $V$  is the minute volume flow of blood through the lungs, and  $T$ , the *mean* pulmonary blood velocity in seconds. If two of the factors are known, the third can be calculated. Were von Kries and Tigerstedt correct in their contention that the speed of the fastest particle as expressed by the "circulation time" is twice the mean velocity, substitution of the pulmonary circulation time for  $T$ , the mean velocity time, would result in magnifying  $Q$ , the quantity of blood in the lungs, which would then become twice too great. If on the contrary, the pulmonary circulation time is an index of the mean velocity, the substitution should give a result which conforms to the results of animal experiments.

#### METHODS AND RESULTS

The crude pulmonary circulation time was measured according to the method previously described (5). The actual pulmonary circulation time, that is to say, the time interval between the arrival of the active deposit of radium in the pulmonary artery and its arrival in the left auricle was estimated by subtracting four seconds from the crude pulmonary circulation time. Four seconds includes the time the active deposit consumes in passing through the heart and varies according to the phase of the cardiac cycle at which the active deposit enters this organ. The four seconds also accounts for the time necessary for the active deposit to travel from the left ventricle to the antecubital arteries.

The minute volume of pulmonary blood flow was measured by the gasometric method of Field, Bock, Gildea and Lathrop (6). Except in the first few subjects, six to nine "alveolar" and "virtual venous" gas samples were analyzed. Occasional discrepant results due to evident errors of technique were discarded. The respiratory minute volume was measured in all subjects, and in nine of the seventeen subjects, the respiratory quotient, and the total CO<sub>2</sub> elimination per minute were measured after, as well as before, the collection of the

<sup>2</sup> By this phrase is meant "the mean time occupied by the passage of blood through the lungs."

the mean pulmonary blood velocity<sup>2</sup> According to the formula of G N Stewart (3),  $Q$  equals  $\frac{VT}{60}$  where  $Q$  is the quantity of blood in the lungs,  $V$  is the minute volume flow of blood through the lungs, and  $T$ , the *mean* pulmonary blood velocity in seconds If two of the factors are known, the third can be calculated Were von Kries and Tigerstedt correct in their contention that the speed of the fastest particle as expressed by the "circulation time" is twice the mean velocity, substitution of the pulmonary circulation time for  $T$ , the mean velocity time, would result in magnifying  $Q$ , the quantity of blood in the lungs, which would then become twice too great If on the contrary, the pulmonary circulation time is an index of the mean velocity, the substitution should give a result which conforms to the results of animal experiments

#### METHODS AND RESULTS

The crude pulmonary circulation time was measured according to the method previously described (5) The actual pulmonary circulation time, that is to say, the time interval between the arrival of the active deposit of radium in the pulmonary artery and its arrival in the left auricle was estimated by subtracting four seconds from the crude pulmonary circulation time Four seconds includes the time the active deposit consumes in passing through the heart and varies according to the phase of the cardiac cycle at which the active deposit enters this organ The four seconds also accounts for the time necessary for the active deposit to travel from the left ventricle to the antecubital arteries

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TABLE 1  
*Measurement of the pulmonary blood velocity, the minute volume blood flow through the lungs, and the quantity of blood in the lungs*

| Number | Date               | Age | Vital capacity | Vital capacity per square meter | Respiratory minute volume | Respiratory quotient | Alveolar CO <sub>2</sub> tension                            | Average alveolar CO <sub>2</sub> tension | 'Virtual' venous CO <sub>2</sub> tension    | Average 'virtual' CO <sub>2</sub> tension | Difference arterial and venous CO <sub>2</sub> content | CO <sub>2</sub> elimination per minute | Circulation rate         | Arm to heart circulation time | Crude pulmonary circulation time | Actual pulmonary circulation time | Amount blood in lungs | Weight of patient | Calculated blood volume | Total blood in lungs |
|--------|--------------------|-----|----------------|---------------------------------|---------------------------|----------------------|---|--|---|---|--|--|--------------------------|-------------------------------|----------------------------------|-----------------------------------|-----------------------|-------------------|-------------------------|----------------------|
| 1      | 1927<br>February 2 | 17  | 4,300          | 2,690                           | 10.5                      |                      | vol. times per cent<br>6.06<br>5.76<br>6.11<br>6.11<br>6.20 | vol. times per cent<br>6.05              | vol. times per cent<br>6.87<br>7.03<br>7.16 | vol. times per cent<br>7.02               | vol. times per cent<br>2.60                            | cc<br>220                              | liters per minute<br>8.5 | seconds<br>55.5               | seconds<br>59.5                  | seconds<br>5                      | cc<br>750             | kgm<br>51.0       | cc<br>3,920             | per cent<br>19       |
| 2a     | February 4         | 36  | 3,250          | 1,957                           | 8.3                       |                      | 5.91<br>5.89<br>5.96<br>5.98                                | 5.94                                     | 6.77<br>6.90<br>7.08<br>7.20                | 6.99                                      | 2.82   | 208                                    | 7.4                      | 13                            | 12                               | 8                                 | 920                   | 58.0              | 4,460                   | 21                   |
| 2b     | February 5         | 36  | 3,250          | 1,957                           | 8.6                       |                      | 5.78<br>5.76<br>5.73<br>5.62                                | 5.72                                     | 6.91<br>6.88<br>7.18                        | 6.88                                      | 3.16   | 205                                    | 6.5                      |                               |                                  |                                   |                       |                   |                         |                      |

TABLE 1  
*Measurement of the pulmonary blood velocity, the minute volume blood flow through the lungs, and the quantity of blood in the lungs*

| Number | Date               | Age | Vital capacity | Vital capacity per square meter | Respiratory volume | Respiratory quotient | Alveolar CO <sub>2</sub> tension                           | Average alveolar CO <sub>2</sub>           | 'Virtual' venous CO <sub>2</sub>         | Average 'virtual' CO <sub>2</sub> | Difference arterial and venous CO <sub>2</sub> content         | CO <sub>2</sub> elimination per minute | Circulation rate         | Arm to heart circulation time | Crude pulmonary circulation time | Actual pulmonary circulation time | Amount blood in lungs | Weight of patient | Calculated blood volume | Total blood in lungs |
|--------|--------------------|-----|----------------|---------------------------------|--------------------|----------------------|--|--|--|-----------------------------------|--|--|--------------------------|-------------------------------|----------------------------------|-----------------------------------|-----------------------|-------------------|-------------------------|----------------------|
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| 2a     | February 4         | 36  | 3,250          | 1,957                           | 8.3                |                      | 5.91<br>5.89<br>5.96<br>5.98                               | 5.94<br>6.77<br>6.90<br>7.08               | 6.77                                     | 6.99                              | 2.82   | 208                                    | 7.4                      | 13                            | 12                               | 8                                 | 920.58                | 0.4               | 4,460                   | 21                   |
| 2b     | February 5         | 36  | 3,250          | 1,957                           | 8.6                |                      | 5.78<br>5.76<br>5.73<br>5.62                               | 5.72<br>6.91<br>6.88<br>7.18               | 6.91                                     | 6.88                              | 3.16   | 205                                    | 6.5                      |                               |                                  |                                   |                       |                   |                         |                      |



TABLE 1—Continued

| Number | Date                | Age | Vital capacity | Vital capacity per square meter | Respiratory minute volume | Respiratory quotient | Alveolar CO <sub>2</sub> tension                             | Average alveolar CO <sub>2</sub> tension | "Virtual" venous CO <sub>2</sub> tension                     | Average "virtual" CO <sub>2</sub> tension | Difference arterial and venous CO <sub>2</sub> content | CO <sub>2</sub> elimination per minute | Circulation rate | Arm to heart circulation time | Crude pulmonary circulation time | Actual pulmonary circulation time | Amount blood in lungs | Weight of patient | Calculated blood volume | Total blood in lungs |
|--------|---------------------|-----|----------------|---------------------------------|---------------------------|----------------------|--|--|--|---|--|--|------------------|-------------------------------|----------------------------------|-----------------------------------|-----------------------|-------------------|-------------------------|----------------------|
| 7      | 1927<br>February 23 | 21  | 4,900          | 2,662                           | 8.9                       |                      | 5.72<br>5.41<br>5.67<br>5.76<br>5.69<br>5.58<br>5.52<br>5.70 | 5.63                                     | 6.54<br>6.68<br>6.91<br>6.46<br>6.88<br>6.69<br>6.36<br>6.58 | 6.64                                      | 2.76   | 308                                    | 11.1             | 8                             | 12.5                             | 8.5                               | 51,558                | 68.9              | 5,300                   | 29                   |
| 8      | February 26         | 21  | 4,100          | 2,611                           | 6.4                       |                      | 6.18<br>6.10<br>6.45<br>5.93<br>6.37                         | 6.20                                     | 7.24<br>7.24<br>6.97<br>7.05<br>6.86<br>6.98<br>7.29<br>7.46 | 7.14                                      | 2.31   | 159                                    | 6.9              | 5.5                           | 11.5                             | 7.5                               | 864                   | 53.4              | 4,108                   | 21                   |

TABLE 1—Continued

| Number | Date                | Age | Vital capacity | Vital capacity per square meter | Respiratory volume | Respiratory quotient | Alveolar CO <sub>2</sub> tension                             | Average alveolar CO <sub>2</sub> tension | "Virtual" venous CO <sub>2</sub> tension                     | Average "virtual" CO <sub>2</sub> tension | Difference arterial and venous CO <sub>2</sub> content | CO <sub>2</sub> elimination per minute | Circulation rate | Arm to heart circulation time | Crude pulmonary circulation time | Actual pulmonary circulation time | Amount blood in lungs | Weight of patient | Calculated blood volume | Total blood in lungs |
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On the basis of our data, and assuming that the total blood volume of man is one-thirteenth of the body weight, the percentage of the total blood in the lungs was calculated. Wide variations were found in the amounts of blood in the lungs, the greater amounts were generally associated with slower blood flow. The average amount of blood in the lungs was, as has been said, 21 per cent of the total blood volume. No great weight is to be attached to the absolute values obtained though the results conform in general to those observed experimentally in animals. G. N. Stewart (3) observed that when both sides of the heart were completely obstructed simultaneously, the lungs in two animals contained respectively 21 and 18.6 per cent of the total blood volume. Similarly, Kuno (7), studying the heart lung preparation under various conditions found from 8.8 to 19.4 per cent of the total blood in the lungs. In animals, by using the pulmonary circulation time as a measure of the mean velocity, Stewart found 11 to 24 per cent of the total blood in the lungs. The average amount was 17 per cent.

On the basis of the data presented in this communication the estimated amount of blood in the lungs in man conforms so closely to the experimental results of Kuno and Stewart as to indicate that the pulmonary circulation time is an index of the mean time of blood flow through the lungs.

The fact that the pulmonary circulation time is such a close index of the mean time consumed by blood flow through the lungs, also indicates that "stringing out" effects caused by variations in the speed of blood flow through different pathways is not of great consequence in normal individuals, and that the different available pathways through the lungs are approximately equal.

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tomatology Mason (14) reported similar results in a case of nephritis of the azotemic type In another communication (15) three cases of chronic nephrosis treated with parathyroid extract are reported from the clinical viewpoint The present communication concerns some observations on the calcium metabolism of two of these cases A summary of the history of these patients is appended

*Case I* I H, female, aged 4 Admitted in August, 1925, with general anasarca No history of previous infections, and apparently well until three days before admission, when edema first appeared in the feet, rapidly extending to involve the whole body

*Physical examination* Marked general anasarca, tonsils enlarged, not inflamed Sinuses negative Heart not enlarged Blood pressure 106/78 Liver just palpable beneath costal margin Fundi normal Urine—albumin 15 grams per liter, granular casts, leucocytes Specific gravity 1014–1022 Blood non-protein nitrogen 25 mgm per 100 cc Total protein 5.05 per cent Albumin globulin ratio 1:3.2 Cholesterol 425 mgm per 100 cc Calcium 5.7 mgm per 100 cc Wassermann negative Slight anemia

At the time the present observations were made there had been no appreciable change in the general condition for some six months in spite of various therapeutic procedures

*Case II* R F, male, age 20 Admitted in September, 1926, with general anasarca Was unaware of any renal disease until September, 1925, when life insurance was refused because of albuminuria No history of infections except "Grippe" Edema began in February, 1926, and had been increasing up to time of admission

*Physical examination* General anasarca, heart not enlarged Vessels not sclerosed Blood pressure 142/92 Fundi negative Urine—albumin 11 grams per liter, hyaline and granular casts Specific gravity varied from 1014–1018, nocturnal polyuria, specific gravity 1012 Urea concentration 1.48 per cent Factor 21.3 (MacLean) Blood urea nitrogen 20.7 mgm per 100 cc Calcium 8.7 mgm per 100 cc Blood proteins 5.49 per cent Albumin globulin ratio 1:2 Cholesterol 500 mgm per 100 cc Basal metabolic rate—30.4 per cent Wassermann negative

#### GENERAL METHODS

Each patient was supplied a weighed diet of general nature, the composition of which remained unchanged during the whole course of the experimental period In case I occasional portions of food not eaten at meal time were fed during the course of the day, in case II all the diet was eaten at meals Under these conditions the

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The urine was collected under toluol in 24-hour amounts starting at 6 a m , the completeness of collection was checked by daily creatinine determinations In case II these values were practically constant, in case I, where the daily values did not check, the daily averages for each complete period agreed closely This was apparently due to the fact that owing to incomplete emptying of the bladder at the end of each 24-hour period, the collections for these periods were incomplete, however, when collections were extended over five days, this error became minimized and a daily average was arrived at

At the beginning and end of each period 0.3 gram carmine was given by mouth at 6 a m , and all stools from the first appearance of the dye up to the appearance of the second dose were collected and included in that period The total resulting stool was evaporated on a water bath, dried to constant weight in an oven at 100°C , ground to a fine powder, and thoroughly mixed, aliquot portions of this powder were taken for the various analyses

Blood for calcium determination was drawn from the antecubital veins twelve hours after the administration of parathyroid extract, allowed to clot, and the serum separated as soon as possible by centrifugalization

#### CHEMICAL METHODS

Calcium in the serum was estimated by Fiske's modification of Kramer and Tisdall's method (17) The calcium in the urine was determined on volumes of 25 cc , evaporated to dryness, ashed in the muffle furnace at faint red heat, and made up to the original volume in solution in 0.1 N HCl Ten cubic centimeters of this solution was measured into a centrifuge tube, 4 cc of saturated solution of ammonium oxalate added, and the reaction then adjusted to the turning point of methyl red (approximately pH 5) by the addition of ammonium hydroxide The procedure was then carried out as for the serum

In the case of the stools, 1 gram of finely powdered dried feces was ashed and made up to 100 cc volume similarly to the urine The calcium in aliquot parts of this solution was then determined as above

All ashings and precipitations were carried out in duplicate, and only results which checked were accepted

#### DISCUSSION

The most striking feature is the extremely small amount of calcium excreted during the control period in the urine of these patients,

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and calcium lactate were given together, there was a definite increase approaching the minimum value found by Sherman (21) in normal children of similar age. A like effect, however, was not obtained in case II, an adult.

In the low urinary excretion of calcium these subjects resemble the subject of Bergeim, Stewart and Hawk (23), who after thyroparathyroidectomy, showed an average daily output of 9.3 mgm. in the urine. A similarly reduced excretion in children suffering from nephritis and from nephrosis has been reported by Boyd, Courtney and MacLachlan (22), and in several nephritics, apparently in uremic states, by Halverson, Mohler, and Bergeim (5).

In this connection the observations of Hetényi and Nógrádi (24) are of interest. These authors found that after the intravenous injection of calcium salts, the excretion in the urine of nephritic subjects was much less than in normal controls, their subjects, however, like those of Halverson, appear to have been of the azotemic, rather than the nephrotic, type.

On the other hand, Hunter and Aub (19) have shown that in cases of lead poisoning, with presumably normal renal function, there was a marked increase in the calcium excreted in the urine when parathyroid extract was administered, the increase averaging 83 per cent above that of the control period. Greenwald and Gross (25) have demonstrated that dogs receiving daily doses of parathyroid extract showed a marked increase in calcium excretion, the greatest increase being in the urine, and to a lesser extent in the stool. These various investigators used, over long periods of time, doses of approximately the same average size as those used in our subjects, and the increased excretion in the urine began almost simultaneously with the administration of parathyroid extract. Our case I, a child weighing 17 kgm., including edema, received 50 units of Collip's extract daily, actually a much larger dose per kilogram of body weight than that administered in the cases of lead poisoning.

It would therefore seem probable that in these cases of nephrosis there is a definite impairment of the ability of the kidney to excrete calcium, an impairment which is not overcome by the use of parathyroid extract, even when the level of calcium in the blood is raised to the normal.

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It is possibly of significance that in both cases increases in the serum calcium were associated with increased excretion in the feces

#### COMMENT

In view of the recent studies of Aub and Bauer (26), who have shown that in myxedema the excretion of calcium is less than in the normal individual, whereas in hyperthyroid states it is greater, it is of interest to note that in both of these patients the basal metabolic rate was much below normal ( $-20$  to  $-30$  per cent), a typical finding in nephrosis first pointed out by Epstein (27). It is possible that their low calcium excretion is due to a mechanism similar to that acting in the myxedema cases of Aub and Bauer (26). Unfortunately no studies of calcium excretion were made while these patients were under thyroid therapy.

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glomerular nephritis with marked renal injury changes also occur as a result both of retention of acid (chiefly phosphoric and sulfuric, occasionally also hydrochloric) and loss of plasma fixed base, dependent primarily upon the failure of the kidney to excrete acid neutralized by ammonia and secondarily upon a failure of the kidney to secrete urine of the normal maximum acidity, (3) that as total electrolyte diminishes in the plasma, non-protein nitrogen increases so that the osmotic pressure remains normal, (4) that consequently, the alteration in the concentration and composition of plasma electrolyte and not the concentration of non-protein nitrogen should be considered as the more important result of renal insufficiency

The chemical methods were the same as described previously (2) In an attempt to calculate the equivalent *osmolar* concentration of the individual electrolytes and non-electrolyte crystalloids from their molar concentration, advantage was taken of the following facts and assumptions

(1) According to Landolt and Bornstein (4), the molecular lowering of the freezing point of NaCl is  $3.45^{\circ}\text{C}$ , which would make the osmolar concentration by volume 1.87 times the molar

(2) According to the same authors, the molecular lowering of the freezing point of  $\text{NaHCO}_3$  is  $3.59^{\circ}\text{C}$  which would make its osmolar concentration by volume 1.95 times the molar

(3) The molecular lowerings, according to the same authors, of  $\text{Na}_2\text{HPO}_4$  and  $\text{NaH}_2\text{PO}_4$  are  $5.0^{\circ}\text{C}$  and  $3.59^{\circ}\text{C}$ , respectively If we assume that the ratio  $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$  remains 4/1, the osmolar concentration by volume of the serum inorganic phosphate can be calculated by multiplying the concentration of inorganic phosphate in mgm per cent by the factor 1.02

(4) The osmotic effect of the protein we considered as being equivalent to that of undissociated B-protein (calculated by Van Slyke's (5) formula for human blood)

(5) Lactic acid was considered as being present in the form of Na lactate, with the same degree of dissociation as NaCl Its osmolar concentration by volume, therefore, would be 1.87 times its molar

(6) The osmotic effect of non-protein nitrogen was assumed to be due entirely to urea and was calculated on the assumption that 70 per cent of the non-protein nitrogen was urea nitrogen The remainder was not taken into account

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## ACUTE HEMORRHAGIC NEPHRITIS

*Protocols*

*Cases 1 to 16, inclusive* These cases were typical uncomplicated cases of acute hemorrhagic nephritis, without uremia, marked edema, or marked vomiting

*Case 17* Cletus B Age, 9 years This patient was admitted on May 12, 1927 Three weeks previously edema was noted, which steadily increased He complained of headache, nausea, vomited occasionally and during the night before admission had two generalized convulsions When admitted he was quite drowsy There was general anasarca His blood pressure was 187/100 mm Hg There was moderate fever and leucocytosis The mucous membrane of his nose was reddened, particularly over the left middle turbinate The tonsils were enlarged and red Frequent convulsions occurred during the first twenty-four hours, despite the free use of sedatives A very small amount of urine, containing many red blood cells, leucocytes and casts was passed during this period Two hundred fifty cubic centimeters of 20 per cent glucose were given intravenously, and there followed a very marked improvement Convulsions ceased, diuresis occurred, edema was rapidly lost, the urine cleared and on May 17 when the patient left the hospital there was only a faint albuminuria

*Case 18* Rose M Age, 14 years This patient had been well until about two weeks before hospital admission on March 28, 1928 She then became ill with fever, cough and headache A week later edema of her face, feet and abdomen were noted This edema largely subsided after about four or five days Her urine was not examined during that time On March 27 three generalized convulsions occurred, each lasting several minutes When first seen at the hospital she was without edema, fever or other signs of acute infection, but much disoriented Her blood pressure was 162/108 mm Hg Her urine showed considerable albumin and many red blood cells, white blood cells and casts Two more generalized convulsions occurred before blood was taken for chemical examination One hundred forty cubic centimeters of 1 per cent magnesium sulfate solution were then given intravenously, after which she became quiet and had no more convulsions The blood pressure gradually returned to normal by April 5 On April 14 the urine was free from albumin and blood cells and showed but an occasional cast and the patient was discharged

*Case 19* Tom F Age, 5 years Except for frequent colds, this patient was well until about October 8, 1926, when edema of the eyelids was noted A few days later, the scrotum became edematous, and on October 20 he was admitted to the hospital He then had generalized edema and ascites The urine contained a large amount of albumin and many leucocytes and red blood cells His tonsils and adenoids were hypertrophied and infected, pus was present in the nose and

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TABLE I

The composition of the blood serum in cases of acute hemorrhagic nephritis

| Case   | Date             | NaCl         | CO <sub>2</sub> content | pH   | Protein  | Inorganic P  | Ca           | Lactic acid* | Glucose*     | N P N *      | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure | Observed osmotic pressure | Remarks                                      |
|--|------------------|--------------|-------------------------|------|----------|--------------|--------------|--------------|--------------|--------------|------------|-----------------------|-------------------|-----------------------------|---------------------------|--|
| Typical uncomplicated cases (1-16 inclusive) |                  |              |                         |      |          |              |              |              |              |              |            |                       |                   |                             |                           |  |
|  |                  | mgm per cent | vol umes per cent       |      | per cent | mgm per cent | mgm per cent | mgm per cent | mgm per cent | mgm per cent | mM         | mM                    | mM                | mM                          | mM                        |  |
| Maximum value                                |                  | 638          | 65.5                    | 7.48 | 9.56     | 8.4          | 14.1         | 27.7         | 148          | 86.0         | 149        | 148                   | 8.0               | 307                         | 337                       |  |
| Minimum value                                |                  | 503          | 34.5                    | 7.35 | 5.47     | 2.0          | 9.5          | 11.3         | 58           | 25.0         | 140        | 134                   | -3.0              | 273                         | 280                       |  |
| Average value                                |                  | 569          | 53.0                    | 7.39 | 7.12     | 5.6          | 11.0         | 22.1         | 104          | 45.7         | 144        | 141                   | 2.7               | 291                         | 310                       |  |
| Number of determinations                     |                  | 26           | 25                      | 23   | 26       | 17           | 8            | 16           | 23           | 26           | 11         | 15                    | 11                | 15                          | 5                         |  |
| Cases with acute uremic convulsions          |                  |              |                         |      |          |              |              |              |              |              |            |                       |                   |                             |                           |  |
| Cletus B<br>No 17                            | May 12, 1927     | 623          | 28.1                    | 7.13 | 6.55     | 4.2          | 12.4         | 110          | 223          | 43.3         | 139        | 145                   | -6.0              | 307                         |                           | Marked edema and elevation of blood pressure |
|  | May 13, 1927     | 591          | 40.2                    | 7.39 | 6.55     | 5.9          |              | 36.7         | 130          | 58.3         |            | 139                   |                   | 292                         |                           | Urine strongly acid                          |
| Rose M<br>No 18                              | March 29, 1928   | 597          | 48.7                    | 7.32 | 7.20     | 4.6          |              | 40.3         | 109          | 29.0         | 163        | 144                   | 19.0              | 293                         |                           | Ammonia present in large amount              |
|  |                  |              |                         |      |          |              |              |              |              |              |            |                       |                   |                             |                           | No edema                                     |
|  |                  |              |                         |      |          |              |              |              |              |              |            |                       |                   |                             |                           | Blood pressure elevated                      |
| Cases with marked oliguria and edema         |                  |              |                         |      |          |              |              |              |              |              |            |                       |                   |                             |                           |  |
| Tommie T<br>No 19                            | October 23, 1926 | 562          | 54.9                    | 7.37 | 5.03     | 5.9          | 9.3          |              | 82           | 36.3         | 137        | 135                   | 2.0               | 278                         |                           | Marked edema                                 |
|  | October 25, 1926 | 561          | 48.9                    | 7.35 | 5.25     | (5.9)        |              | 39.2         |              | 38.3         |            |                       |                   |                             |                           | Moderate edema                               |
|  | November 2, 1926 | 567          | 56.1                    | 7.40 | 6.34     |              | 9.1          |              | 87           | 32.3         |            |                       |                   |                             |                           |  |
|  | November 8, 1926 | 585          | 46.7                    | 7.36 | 6.34     |              |              |              |              |              |            |                       |                   |                             |                           |  |

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blood are shown in table 1 and chart 1. During the next five days, there was irregular fever, the temperature fluctuating from 37°C to 39.3°C. The leucocyte count rose from 10,800 on admission to 21,000 on April 14. Persistent vomiting continued. On April 14, both antra were irrigated, pus being washed out, and the left mastoid was opened, pus also being found. From both the mastoid and the blood stream *Streptococcus hemolyticus* was cultured. Following mastoidectomy, vomiting ceased immediately. A marked skin eruption of the erythema multiforme type appeared. The patient's condition steadily improved, despite the fact that the septicemia persisted until April 20 and that an abscess, probably embolic, developed in the chest wall. Following tonsillectomy and adenoidectomy on May 21, fever and gross hematuria recurred, lasting for a week. The maxillary antra were treated by repeated irrigations. The patient was then sent to the country department of the hospital for convalescence. There her temperature became normal, her urine cleared completely, and she gained 30 pounds in weight in 9 months.

Therapy directly influencing the composition of the blood studied was as follows:

On April 12, after the first blood sample was obtained, 900 cc. of Ringer's solution were given intraperitoneally, and 400 cc. of 10 to 20 per cent glucose intravenously. After the second blood sample on the same day, 1500 cc. of Ringer's solution and 100 cc. of glucose were given. On April 14, 400 cc. of Ringer's solution were given intraperitoneally and 250 cc. of glucose solution intravenously. On April 15, 175 cc. of blood, and on April 21, 180 cc. of blood were given intravenously.

*Case 22* Luella R. Age, 5 years. This patient was admitted on December 3, 1921. A month previously, she had complained of earache and had fever. A week before admission there was a spontaneous rupture of one ear drum. Hematuria and marked vomiting were present for three days before admission. On admission, the patient was desiccated and had slight fever. The urine contained gross blood, much albumin and many casts. The tonsils were large and ragged and the left ear was discharging pus through a good sized perforation. With rest in bed and restricted diet, the general condition improved, the urine cleared, and on April 22 the tonsils and adenoids were removed.

*Case 23* Tommie M. Age, 6 years. This patient had been well until he was injured during a tornado in the latter part of September, 1927. He received many skin wounds, which later became infected. About the first of November, blood was noted in his urine, slight fever was present and vomiting became very marked. A week later, November 8, 1927, he was admitted to the hospital. He was found to be undernourished and with several infected skin wounds and many scars of wounds already healed. The tonsils were ragged and red and there was considerable pus seen in his nose. His urine showed gross blood and a large amount of albumin. With rest in bed and restricted diet, his urine gradually cleared and became negative on December 12, at which time he was discharged on a regular diet.

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22.1 Glucose varied from 58 to 148 mgm per cent. Total base varied only from 140 to 149, averaging 144 mM. "Total" acid ( $\text{Cl} + \text{HCO}_3 + \text{protein} + \text{HPO}_4 + \text{lactic acid}$ ) varied somewhat more, from 134 to 148 mM, averaging 141. Undetermined acid varied from -3.0 to 8.0, averaging 2.7 mM. By freezing point determinations, in five instances the osmotic pressure averaged 310 mM, varying between 280 and 337. The calculated osmotic pressure varied from 273 to 307, averaging 291 mM, or 94.0 per cent of the average determined osmotic pressure, a normal relationship. Non-protein nitrogen varied from 25 to 86 mgm per cent, averaging 45.7.

#### *Cases with acute uremic convulsions*

Case 17, whose blood was studied shortly after uremic convulsions had occurred, showed a marked "acidosis." The  $\text{BHCO}_3$  content was reduced by 11 mM and was almost exactly equalled by the 10.2 mM increase in lactic acid. The pH had dropped to 7.13. BCl was increased by 7 mM. There was also hyperglycemia, the glucose content being 223 mgm per cent. On the next day, with cessation of convulsions, there was noted an increase in  $\text{BHCO}_3$  of 5.1 mM with a decrease of 8.1 mM lactic acid and 6 mM BCl. As calculated, about 6 mM electrolyte had left the blood stream. Diuresis had not yet begun, and edema was apparently increasing during this period. The lactic acid "acidosis" in this instance undoubtedly occurred as a result of the convulsions and anoxemia present at and before the time that the blood was studied.

Case 18 was a similar case and similarly showed decrease in  $\text{BHCO}_3$  and increase in lactic acid. An unusually high value for undetermined acid, 19.0 mM, was indicated, however. Total base in this instance was unusually high, and may have been in error, and such a large quantity of undetermined acid may not really have existed.

It is rather interesting to note that in Case 17 the non-protein nitrogen during the acute uremic manifestations was but 43.3 mgm per cent, and in Case 18 but 29 mgm per cent.

#### *Cases with marked oliguria and edema*

Case 19, when admitted was at first mistaken for nephrosis. Edema and albuminuria were very marked, and there was neither non-protein

22.1 Glucose varied from 58 to 148 mgm per cent. Total base varied only from 140 to 149, averaging 144 mM. "Total" acid ( $\text{Cl} + \text{HCO}_3 + \text{protein} + \text{HPO}_4 + \text{lactic acid}$ ) varied somewhat more, from 134 to 148 mM, averaging 141. Undetermined acid varied from -3.0 to 8.0, averaging 2.7 mM. By freezing point determinations, in five instances the osmotic pressure averaged 310 mM, varying between 280 and 337. The calculated osmotic pressure varied from 273 to 307, averaging 291 mM, or 94.0 per cent of the average determined osmotic pressure, a normal relationship. Non-protein nitrogen varied from 25 to 86 mgm per cent, averaging 45.7.

#### *Cases with acute uremic convulsions*

Case 17, whose blood was studied shortly after uremic convulsions had occurred, showed a marked "acidosis." The  $\text{BHCO}_3$  content was reduced by 11 mM and was almost exactly equalled by the 10.2 mM increase in lactic acid. The pH had dropped to 7.13. BCl was increased by 7 mM. There was also hyperglycemia, the glucose content being 223 mgm per cent. On the next day, with cessation of convulsions, there was noted an increase in  $\text{BHCO}_3$  of 5.1 mM with a decrease of 8.1 mM lactic acid and 6 mM BCl. As calculated, about 6 mM electrolyte had left the blood stream. Diuresis had not yet begun, and edema was apparently increasing during this period. The lactic acid "acidosis" in this instance undoubtedly occurred as a result of the convulsions and anoxemia present at and before the time that the blood was studied.

Case 18 was a similar case and similarly showed decrease in  $\text{BHCO}_3$  and increase in lactic acid. An unusually high value for undetermined acid, 19.0 mM, was indicated, however. Total base in this instance was unusually high, and may have been in error, and such a large quantity of undetermined acid may not really have existed.

It is rather interesting to note that in Case 17 the non-protein nitrogen during the acute uremic manifestations was but 43.3 mgm per cent, and in Case 18 but 29 mgm per cent.

#### *Cases with marked oliguria and edema*

Case 19, when admitted was at first mistaken for nephrosis. Edema and albuminuria were very marked, and there was neither non-protein

as well as non-protein nitrogen was noted. On November 29, however, a few days after a decided diuresis with loss of edema fluid had begun, an interesting chemical picture was noted.  $\text{BHCO}_3$  was still reduced, but BCl was decidedly higher than normal. Total acid was slightly above the normal and non-protein nitrogen had dropped almost to the normal value. A normal freezing point at this time was observed and agreed well with the calculated one.

*Cases with marked vomiting and dehydration*

Case 21 was admitted after two weeks of marked vomiting and one week of hematuria, the results of a hemolytic streptococcic infection of one mastoid and both maxillary antra. Severe dehydration was present. The blood picture on admission was extremely interesting. BCl was greatly reduced, being but 71 mM.  $\text{BHCO}_3$  was of a low normal concentration, 21.0 mM. The pH was 7.35. Protein concentration was 7.96 per cent, as compared with 5.24 per cent following restoration of a normal fluid balance, thus indicating marked water loss from the plasma. Inorganic phosphate was very much increased and calcium considerably decreased. Total base was also considerably reduced, 127 mM, and exceeded "total" acid by 7.0 mM. The undetermined acids were presumably sulfuric and lactic. The total electrolyte osmolar concentration as calculated was only 227 mM. Non-protein nitrogen, however, was so elevated (250 mgm per cent) that the *total* osmolar concentration as calculated was 301 mM, in very good agreement with the observed freezing point indicating a concentration of 308 mM. The administration of 900 cc of Ringer's solution and 400 cc of 10 per cent glucose on the day of admission effected a considerable dilution of the plasma, judging from the fall of plasma protein from 7.96 to 7.03 per cent, but vomiting persisted and BCl remained low, while  $\text{BHCO}_3$  increased to 28.1 mM. Inorganic phosphate reached the enormous value of 24.5 mgm per cent, and calcium the low value of 3.6 mgm per cent. The total electrolyte osmolar concentration was little altered, being but 230 mM, and the non-protein nitrogen remained elevated. As before, the freezing point indicated a normal osmotic pressure (309 mM).

With further administration of Ringer's solution, there occurred an increase in BCl to 810 mM on April 14 sufficient to raise the elec-

as well as non-protein nitrogen was noted. On November 29, however, a few days after a decided diuresis with loss of edema fluid had begun, an interesting chemical picture was noted.  $\text{BHCO}_3$  was still reduced, but BCl was decidedly higher than normal. Total acid was slightly above the normal and non-protein nitrogen had dropped almost to the normal value. A normal freezing point at this time was observed and agreed well with the calculated one.

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With further administration of Ringer's solution, there occurred an increase in BCl to 810 mM on April 14 sufficient to raise the elec-



TABLE 2  
*The composition of the blood serum in cases of sub acute and chronic glomerular nephritis*

| Case                  | Date             | NaCl         | CO <sub>2</sub> content | pH     | Protein  | Inorganic P  | Ca           | Lactic acid*  | Glucose*     | N P N *      | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure | Observed osmotic pressure | Remarks   |
|-----------------------|------------------|--------------|-------------------------|--------|----------|--------------|--------------|---------------|--------------|--------------|------------|-----------------------|-------------------|-----------------------------|---------------------------|---|
|                       |                  | mgm per cent | vol umes per cent       |        | per cent | mgm per cent | mgm per cent | mgm. per cent | mgm per cent | mgm per cent | mlf        | mlf                   | mlf               | mlf                         | mlf                       |   |
| Elizabeth Z.<br>No 24 | January 12, 1925 | 597          | (50.0)                  | (7.40) | 5.03     | (6.0)        |              | (18.0)        | 110          | 71.0         |            | 140                   |                   | 297                         |                           | Moderate edema and elevation of blood pressure Urine strongly acid, containing chloride and ammonia |
|                       | April 8, 1925    | 585          | (50.0)                  | (7.40) | 5.25     | (6.0)        |              | (18.0)        |              | 44.0         |            | 138                   |                   | 282                         |                           | No edema Blood pressure 130/80  |
|                       | April 9, 1925    | 516          | (40.0)                  | (7.35) | 3.50     | (9.0)        |              | (18.0)        |              | 57.0         |            | 123                   |                   | 261                         |                           | Slight edema Blood pressure 88/40   |
|                       | April 11, 1925   | 480          | 11.2                    | (7.20) | 5.25     | 13.2         |              | (18.0)        |              | 89.0         |            | 108                   |                   | 234                         |                           | Marked edema Blood pressure 90/60   |
|                       | April 13, 1925   | 471          | 35.3                    | (7.30) | 5.47     | 14.4         |              | (18.0)        |              | 152          |            | 116                   |                   | 268                         |                           | Marked edema Blood pressure 110/82  |
|                       | April 14, 1925   | 456          | 42.4                    | (7.35) | 6.58     | 12.0         |              | (18.0)        |              | 191          |            | 119                   |                   | 288                         |                           | No edema  |
|                       | April 14, 1925   | 517          | 38.1                    | (7.35) | 6.12     | 14.4         |              | (18.0)        |              | 200          |            | 127                   |                   | 300                         |                           | Urine from April 11 to May 11 contained but very little chloride or ammonia and was strongly acid   |
|                       | April 15, 1925   | 512          | 38.3                    | (7.35) | 6.12     | 10.8         |              | (18.0)        |              | 225          |            | 125                   |                   | 304                         |                           |   |
|                       | April 18, 1925   | 514          | 40.6                    | (7.35) | 6.12     | 11.6         |              | (18.0)        |              | 190          |            | 125                   |                   | 297                         |                           |   |
|                       | April 20, 1925   | 512          | (41.0)                  | (7.35) | (6.23)   | (10.0)       |              | (18.0)        |              | 112          |            | 126                   |                   | 275                         |                           |   |
|                       | April 23, 1925   | 527          | (41.0)                  | (7.35) | 6.34     | (10.0)       |              | (18.0)        |              | 102          |            | 128                   |                   | 279                         |                           |   |
|                       | April 27, 1925   | 519          | (41.0)                  | (7.35) | 8.49     | (8.0)        |              | (18.0)        |              | 99.0         |            | 130                   |                   | 282                         |                           |   |
|                       | April 29, 1925   | 505          | 43.0                    | (7.35) | (8.06)   | (8.0)        |              | (18.0)        |              | 66.0         |            | 128                   |                   | 267                         |                           |   |
|                       | May 3, 1925      | 521          | 44.3                    | (7.35) | (7.63)   | (8.0)        |              | (18.0)        |              | 96.0         |            | 130                   |                   | 282                         |                           | Very slight edema Blood pressure 136/112  |
|                       | May 8, 1925      | 479          | 39.6                    | (7.35) | 7.20     | (8.0)        |              | (18.0)        |              | 82.0         |            | 130                   |                   | 258                         |                           |   |
|                       | May 11, 1925     | 468          | 33.0                    | (7.35) | 6.98     | (8.0)        |              | (18.0)        |              | 89.0         |            | 117                   |                   | 251                         |                           |   |
|                       | May 16, 1925     | 527          | (45.5)                  | (7.35) | 7.55     | 7.6          |              | (18.0)        |              | 72.0         |            | 129                   |                   | 271                         |                           |   |

TABLE 2

The composition of the blood serum in cases of sub acute and chronic glomerular nephritis

| Case                  | Date    | NaCl         | CO <sub>2</sub> content | pH     | Protein       | Inorganic P  | Ca           | Lactic acid*  | Glucose*     | N P N *      | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure | Observed osmotic pressure | Remarks   |
|-----------------------|---------|--------------|-------------------------|--------|---------------|--------------|--------------|---------------|--------------|--------------|------------|-----------------------|-------------------|-----------------------------|---------------------------|---|
|                       |         | mgm per cent | vol umes per cent       |        | per cent      | mgm per cent | mgm per cent | mgm. per cent | mgm per cent | mgm per cent | mmf        | mmf                   | mmf               | mmf                         | mmf                       |   |
| Elizabeth Z.<br>No 24 | January | 12, 1925     | 597 (50.0)              | (7.40) | 5.03          | (6.0)        |              | (18.0)        | 110          | 71.0         |            | 140                   |                   | 297                         |                           | Moderate edema and elevation of blood pressure Urine strongly acid, containing chloride and ammonia |
|                       | April   | 8 1925       | 585 (50.0)              | (7.40) | 5.25          | (6.0)        |              | (18.0)        |              | 44.0         |            | 138                   |                   | 282                         |                           | No edema Blood pressure 130/80  |
|                       | April   | 9, 1925      | 516 (40.0)              | (7.35) | 3.50 (9.0)    |              |              | (18.0)        |              | 57.0         |            | 123                   |                   | 261                         |                           | Slight edema Blood pressure 88/40   |
|                       | April   | 11, 1925     | 480 14.2                | (7.20) | 5.25 13.2     |              |              | (18.0)        |              | 89.0         |            | 108                   |                   | 234                         |                           | Marked edema Blood pressure 90/60   |
|                       | April   | 13, 1925     | 471 35.3                | (7.30) | 5.47 14.4     |              |              | (18.0)        |              | 152          |            | 116                   |                   | 268                         |                           | Marked edema Blood pressure 110/82  |
|                       | April   | 14, 1925     | 456 42.4                | (7.35) | 6.58 12.0     |              |              | (18.0)        |              | 191          |            | 119                   |                   | 288                         |                           | No edema  |
|                       | April   | 14, 1925     | 517 38.1                | (7.35) | 6.12 14.4     |              |              | (18.0)        |              | 200          |            | 127                   |                   | 300                         |                           | Urine from April 11 to May 11   |
|                       | April   | 15, 1925     | 512 38.3                | (7.35) | 6.12 10.8     |              |              | (18.0)        |              | 225          |            | 125                   |                   | 304                         |                           | contained but very little chloride  |
|                       | April   | 18, 1925     | 514 40.6                | (7.35) | 6.12 11.6     |              |              | (18.0)        |              | 190          |            | 125                   |                   | 297                         |                           | or ammonia and was strongly acid  |
|                       | April   | 20 1925      | 512 (41.0)              | (7.35) | (6.23) (10.0) |              |              | (18.0)        |              | 112          |            | 126                   |                   | 275                         |                           |   |
|                       | April   | 23 1925      | 527 (41.0)              | (7.35) | 6.34 (10.0)   |              |              | (18.0)        |              | 102          |            | 128                   |                   | 279                         |                           |   |
|                       | April   | 27, 1925     | 519 (41.0)              | (7.35) | 8.49 (8.0)    |              |              | (18.0)        |              | 99.0         |            | 130                   |                   | 282                         |                           |   |
|                       | April   | 29, 1925     | 505 43.0                | (7.35) | (8.06) (8.0)  |              |              | (18.0)        |              | 66.0         |            | 128                   |                   | 267                         |                           |   |
|                       | May     | 3, 1925      | 521 44.3                | (7.35) | (7.63) (8.0)  |              |              | (18.0)        |              | 96.0         |            | 130                   |                   | 282                         |                           |   |
|                       | May     | 8, 1925      | 479 39.6                | (7.35) | 7.20 (8.0)    |              |              | (18.0)        |              | 82.0         |            | 130                   |                   | 258                         |                           |   |
|                       | May     | 11 1925      | 468 33.0                | (7.35) | 6.98 (8.0)    |              |              | (18.0)        |              | 89.0         |            | 117                   |                   | 251                         |                           |   |
|                       | May     | 16 1925      | 527 (45.5)              | (7.35) | 7.55 7.6      |              |              | (18.0)        |              | 72.0         |            | 129                   |                   | 271                         |                           |   |

TAB E 2—Continued

| Case              | Date               | NaCl         |              | CO <sub>2</sub> content |              | pH     | Protein  | Inorganic P  |              | Ca | Lactic acid* |              | Glucose*     |              | N P % | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure |    | Observed osmotic pressure | Remarks |
|-------------------|--------------------|--------------|--------------|-------------------------|--------------|--------|----------|--------------|--------------|----|--------------|--------------|--------------|--------------|-------|------------|-----------------------|-------------------|-----------------------------|----|---------------------------|---------|
|                   |                    | mgm per cent | mgm per cent | vol per cent            | vol per cent |        | per cent | mgm per cent | mgm per cent |    | mgm per cent | mgm per cent | mgm per cent | mgm per cent |       |            |                       |                   | mM                          | mM |                           |         |
| Marie II<br>No 26 | November 3, 1925   | 608          |              | 31.8                    |              | 7.10   | 8.06     | 9.5          | 6.8          |    | (18.0)       |              | 70           |              | 170   |            | 139                   |                   | 321                         |    |                           |         |
|                   | November 9, 1925   | 614          |              | 32.4                    |              | 7.35   | 7.85     | 9.5          |              |    | (18.0)       |              | 84           |              | 130   |            | 142                   |                   | 313                         |    |                           |         |
|                   | November 17, 1925  | 620          |              | 32.0                    |              | 7.30   | 8.19     | (9.5)        | 6.0          |    | (18.0)       |              | 82           |              | 111   |            | 144                   |                   | 311                         |    |                           |         |
|                   | November 25, 1925  | 550          |              | 31.6                    |              | (7.30) | 6.66     | (9.5)        | 8.3          |    | (18.0)       |              | 106          |              | 117   |            | 129                   |                   | 285                         |    |                           |         |
|                   | December 31, 1925  | 620          |              | 23.4                    |              | (7.30) | 6.67     | (9.5)        | 6.6          |    | (18.0)       |              |              |              | 108   |            | 138                   |                   | 299                         |    |                           |         |
|                   | January 1, 1926    | 585          |              | 19.9                    |              |        |          |              | 8.6          |    | (18.0)       |              |              |              | 107   |            |                       |                   |                             |    |                           |         |
|                   | January 5, 1926    | 491          |              | 22.5                    |              | 7.28   | 7.44     |              | 8.6          |    |              |              | 111          |              | 160   |            |                       |                   |                             |    |                           |         |
|                   | January 8, 1926    | 725          |              | 21.6                    |              | 7.25   | 6.83     | 11.0         | 9.0          |    | (18.0)       |              | 112          |              | 170   |            | 150                   |                   | 347                         |    |                           |         |
|                   | January 11, 1926   | 608          |              | 20.0                    |              | 7.27   | 7.20     | 13.4         | 6.6          |    | (18.0)       |              | 109          |              | 180   |            | 133                   |                   | 320                         |    |                           |         |
|                   | January 25, 1926   | 562          |              | 28.3                    |              | (7.27) | 6.55     |              |              |    | (18.0)       |              | 109          |              | 163   |            |                       |                   |                             |    |                           |         |
|                   | February 3, 1926   | 562          |              | 32.5                    |              | 7.27   | 8.28     | 13.6         |              |    | (18.0)       |              | 122          |              | 60.0  |            | 132                   |                   | 284                         |    |                           |         |
|                   | February 12, 1926  | 596          |              | 36.3                    |              | 7.20   | 8.05     |              | 6.6          |    |              |              | 96           |              | 146   |            |                       |                   |                             |    |                           |         |
|                   | March 18, 1926     | 602          |              | 43.7                    |              | 7.36   | 5.47     | 11.3         | 6.0          |    | (18.0)       |              | 112          |              | 67.0  |            | 140                   |                   | 292                         |    |                           |         |
|                   | April 12, 1926     | 591          |              | 33.2                    |              | 7.23   | 6.25     |              | 7.2          |    |              |              | 130          |              | 112   |            | 133                   |                   | 300                         |    |                           |         |
|                   | May 17, 1926       | 661          |              | 28.5                    |              | (7.25) | 5.57     | 12.6         |              |    |              |              | 103          |              | 101   |            |                       |                   |                             |    |                           |         |
|                   | June 14, 1926      | 649          |              | 33.5                    |              | 7.30   | 5.47     |              |              |    |              |              |              |              |       |            |                       |                   |                             |    |                           |         |
|                   | July 12, 1925      | 670          |              | 34.7                    |              | 7.32   | 5.25     |              | 6.9          |    |              |              | 112          |              | 87.0  |            | 145                   | 13                | 289                         |    |                           |         |
|                   | August 9, 1926     | 573          |              | 31.8                    |              | 7.38   | 5.68     |              | 7.3          |    | (18.0)       |              | 109          |              | 123   |            | 136                   |                   | 285                         |    |                           |         |
|                   | August 23, 1926    | 655          |              | 29.0                    |              | (7.35) | 5.47     | 7.2          |              |    |              |              |              |              | 92.0  |            | 131                   |                   |                             |    |                           |         |
|                   | August 25, 1926    | 612          |              | 32.6                    |              | 7.35   | 5.03     | 6.5          | 6.6          |    | (18.0)       |              |              |              |       |            |                       |                   |                             |    |                           |         |
|                   | August 29, 1926    | 616          |              | 34.8                    |              | 7.35   | 5.25     |              |              |    |              |              | 142          |              | 108   |            | 146                   |                   |                             |    |                           |         |
|                   | September 6, 1926  | 619          |              | 35.8                    |              | 7.37   | 4.48     |              | 7.9          |    |              |              | 96           |              | 96.0  |            | 145                   | 7                 | 289                         |    |                           |         |
|                   | September 14, 1926 | 608          |              | 29.1                    |              | 7.35   | 5.47     | 4.0          |              |    |              |              |              |              | 95.0  |            |                       |                   |                             |    |                           |         |

TABLE 2—Continued

| Case             | Date               | NaCl | CO <sub>2</sub> content | pH     | Protein | Inorganic P | Ca  | Lactic acid* | Glucose* | N P % | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure | Observed osmotic pressure | Remarks |
|------------------|--------------------|------|-------------------------|--------|---------|-------------|-----|--------------|----------|-------|------------|-----------------------|-------------------|-----------------------------|---------------------------|---------|
|                  |                    |      |                         |        |         |             |     |              |          |       |            |                       |                   |                             |                           |         |
| Marie H<br>No 26 | November 3, 1925   | 608  | 31.8                    | 7.10   | 8.06    | 9.5         | 6.8 | (18.0)       | 70       | 170   |            | 139                   |                   | 321                         |                           |         |
|                  | November 9, 1925   | 614  | 32.4                    | 7.35   | 7.85    | 9.5         |     | (18.0)       | 84       | 130   |            | 142                   |                   | 313                         |                           |         |
|                  | November 17, 1925  | 620  | 32.0                    | 7.30   | 8.19    | (9.5)       | 6.0 | (18.0)       | 82       | 111   |            | 144                   |                   | 311                         |                           |         |
|                  | November 25, 1925  | 550  | 31.6                    | (7.30) | 6.66    | (9.5)       | 8.3 | (18.0)       | 106      | 117   |            | 129                   |                   | 285                         |                           |         |
|                  | December 31, 1925  | 620  | 23.4                    | (7.30) | 6.67    | (9.5)       | 6.6 | (18.0)       |          | 108   |            | 138                   |                   | 299                         |                           |         |
|                  | January 1, 1926    | 585  | 19.9                    |        |         |             | 8.6 | (18.0)       |          | 107   |            |                       |                   |                             |                           |         |
|                  | January 5, 1926    | 491  | 22.5                    | 7.28   | 7.44    |             | 8.6 |              | 111      | 160   |            |                       |                   |                             |                           |         |
|                  | January 8, 1926    | 725  | 21.6                    | 7.25   | 6.83    | 11.0        | 9.0 | (18.0)       | 112      | 170   |            | 150                   |                   | 347                         |                           |         |
|                  | January 11, 1926   | 608  | 20.0                    | 7.27   | 7.20    | 13.4        | 6.6 | (18.0)       | 109      | 180   |            | 133                   |                   | 320                         |                           |         |
|                  | January 25, 1926   | 562  | 28.3                    | (7.27) | 6.55    |             |     | (18.0)       | 109      | 163   |            |                       |                   |                             |                           |         |
|                  | February 3, 1926   | 562  | 32.5                    | 7.27   | 8.28    | 13.6        |     | (18.0)       | 122      | 60.0  |            | 132                   |                   | 284                         |                           |         |
|                  | February 12, 1926  | 596  | 36.3                    | 7.20   | 8.05    |             | 6.6 |              | 96       | 146   |            |                       |                   |                             |                           |         |
|                  | March 18, 1926     | 602  | 43.7                    | 7.36   | 5.47    | 11.3        | 6.0 | (18.0)       | 112      | 67.0  |            | 140                   |                   | 292                         |                           |         |
|                  | April 12, 1926     | 591  | 33.2                    | 7.23   | 6.25    |             | 7.2 |              | 130      | 112   |            | 133                   |                   | 300                         |                           |         |
|                  | May 17, 1926       | 661  | 28.5                    | (7.25) | 5.57    | 12.6        |     |              | 103      | 101   |            |                       |                   |                             |                           |         |
|                  | June 14, 1926      | 649  | 33.5                    | 7.30   | 5.47    |             |     |              | 122      | 99.0  |            |                       |                   |                             |                           |         |
|                  | July 12, 1926      | 670  | 34.7                    | 7.32   | 5.25    |             | 6.9 |              | 112      | 87.0  |            | 145                   | 13                | 289                         |                           |         |
|                  | August 9, 1926     | 573  | 31.8                    | 7.38   | 5.68    | 4.5         | 7.3 | (18.0)       | 109      | 123   |            |                       |                   | 285                         |                           |         |
|                  | August 23, 1926    | 655  | 29.0                    | (7.35) | 5.47    | 7.2         |     |              |          | 92.0  |            |                       |                   |                             |                           |         |
|                  | August 25, 1926    | 612  | 32.6                    | 7.35   | 5.03    | 6.5         | 6.6 | (18.0)       |          |       |            |                       | 131               |                             |                           |         |
|                  | August 29, 1926    | 616  | 34.8                    | 7.35   | 5.25    |             |     |              | 142      | 108   |            | 146                   |                   |                             |                           |         |
|                  | September 6, 1926  | 619  | 35.8                    | 7.37   | 4.48    |             | 7.9 |              | 96       | 96.0  |            | 145                   | 128               | 7                           | 289                       |         |
|                  | September 14, 1926 | 608  | 29.1                    | 7.35   | 5.47    | 4.0         |     |              |          | 95.0  |            |                       |                   |                             |                           |         |

TABLE 2—Continued

| Case                | Date              | NaCl         |                    | CO <sub>2</sub> content | pH   | Protein | Inorganic P | Ca | Lactic acid* | Glucose* | N P % | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure | Observed osmotic pressure | Remarks   |
|---------------------|-------------------|--------------|--------------------|-------------------------|------|---------|-------------|----|--------------|----------|-------|------------|-----------------------|-------------------|-----------------------------|---------------------------|---|
|                     |                   | mgm per cent | vol times per cent |                         |      |         |             |    |              |          |       |            |                       |                   |                             |                           |   |
| Margaret Q<br>No 31 | January 4, 1928   | 620          | 44 1               | 7 27                    | 4 16 | 9 0     |             |    | 65 65        | 965      | 47 03 | 139        | 145                   |                   | 297                         | 311                       | Very marked edema Blood pressure elevated Urine pH 6+ Small amounts of ammonia, but considerable chloride |
|                     | January 6 1928    | 626          | 43 0               | 7 45                    | 3 31 | 8 0     |             |    | 21 45        | 945      | 65 58 | 137        | 139                   |                   | 284                         | 310                       |   |
|                     | January 11, 1928  | 585          | 41 9               | 7 43                    | 4 59 | 6 7     |             |    | 32 85        | 1155     | 74 05 |            | 135                   |                   | 283                         |                           |   |
|                     | January 23 1928   | 626          | 53 0               | 7 43                    | 4 16 | 7 0     | 9 4         |    | 17 69        | 1035     | 53 05 | 154        |                       | 297               |                             |                           |   |
|                     | February 10, 1928 | 608          | 51 2               | 7 41                    | 4 59 | 7 9     | 8 5         |    | 13 95        | 1125     | 68 55 |            |                       | 298               |                             | 328                       |   |
| Mr T<br>No 35       | December 14, 1926 | 585          | 49 0               | 7 35                    | 7 85 | 6 4     | 9 9         |    | 13 3         |          | 105   |            | 142                   |                   | 320                         |                           |   |
| Mr T<br>No 36       | January 7, 1928   | 538          | 34 8               | 7 35                    | 7 63 | 10 0    |             |    | 47 85        | 160      | 120   |            | 134                   |                   | 297                         | 322                       | No edema Blood pressure normal Urine pH 6+ Very little ammonia but considerable chloride                  |
|                     | January 10, 1928  | 503          | 34 1               | 7 29                    | 8 06 | 6 3     |             |    | 25 25        | 126      | 134   | 140        | 123                   | 17                | 278                         | 307                       |   |
|                     | January 12 1928   | 519          | 35 5               | 7 27                    | 8 92 | 8 9     | 11 7        |    | 27 75        |          | 140   | 143        | 130                   | 13                | 295                         | 325                       |   |
|                     | January 16, 1928  | 509          | 48 5               | 7 42                    | 6 98 | 7 2     | 11 8        |    | 26 55        | 137      | 113   | 138        | 130                   | 8                 | 286                         | 324                       |   |
|                     | January 26 1928   | 509          | 68 0               | 7 28?                   | 7 42 | 8 5     | 10 0        |    | 39 15        | 110      | 90 7  | 150        | 140                   | 10                | 291                         | 328                       |   |
|                     | February 1, 1928  | 538          | 60 0               | 7 40                    | 7 20 | 5 0     |             |    |              | 85       | 67 0  | 143        | 139                   | 5                 | 294                         | 340                       |   |

\* Whole blood determined except where serum determinations are indicated by postscript (s)

() indicates assumed values.

† N B The inorganic sulfate concentration of 10 0 mM is included

TABLE 2—Continued

| Case                | Date              | NaCl | CO <sub>2</sub> content | pH    | Protein | Inorganic P | Ca   | Lactic acid*      |                  | Glucose*          | N P V *           | Total base | Total determined acid | Undetermined acid | Calculated osmotic pressure | Observed osmotic pressure | Remarks   |
|---------------------|-------------------|------|-------------------------|-------|---------|-------------|------|-------------------|------------------|-------------------|-------------------|------------|-----------------------|-------------------|-----------------------------|---------------------------|---|
|                     |                   |      |                         |       |         |             |      | mgm per cent      | mgm per cent     |                   |                   |            |                       |                   |                             |                           |   |
| Margaret Q<br>No 31 | January 4, 1928   | 620  | 44 1                    | 7 27  | 4 16    | 9 0         |      | 65 6 <sup>s</sup> | 96 <sup>s</sup>  |                   | 47 0 <sup>s</sup> | 139        | 145                   |                   | 297                         | 311                       | Very marked edema Blood pres<br>sure elevated Urine pH 6+<br>Small amounts of ammonia, but<br>considerable chloride |
|                     | January 6 1928    | 626  | 43 0                    | 7 45  | 3 31    | 8 0         |      | 21 4 <sup>s</sup> | 94 <sup>s</sup>  | 65 5 <sup>s</sup> | 137               | 139        |                       | 284               | 310                         |                           |   |
|                     | January 11, 1928  | 585  | 41 9                    | 7 43  | 4 59    | 6 7         |      | 32 8 <sup>s</sup> | 115 <sup>s</sup> | 74 0 <sup>s</sup> | 135               |            | 283                   |                   |                             |                           |   |
|                     | January 23 1928   | 626  | 53 0                    | 7 43  | 4 16    | 7 0         | 9 4  | 17 6 <sup>s</sup> | 103 <sup>s</sup> | 53 0 <sup>s</sup> | 154               |            | 297                   |                   |                             |                           |   |
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| Mr T<br>No 36       | January 7, 1928   | 538  | 34 8                    | 7 35  | 7 63    | 10 0        |      | 47 8 <sup>s</sup> | 160              | 120               | 134               | 140        | 123                   | 17                | 278                         | 307                       | No edema Blood pressure normal<br>Urine pH 6+ Very little am<br>monia but considerable chloride                     |
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|                     | January 26 1928   | 509  | 68 0                    | 7 287 | 7 42    | 8 5         | 10 0 | 39 1 <sup>s</sup> | 110              | 90 7              | 150               | 140        | 10                    | 291               | 328                         |                           |   |
|                     | February 1, 1928  | 538  | 60 0                    | 7 40  | 7 20    | 5 0         |      | 85                | 67 0             | 143               | 139               | 5          | 294                   | 340               |                             |                           |   |

\* Whole blood determined except where serum determinations are indicated by postscript (s)

( ) indicates assumed values.

† N.B. The inorganic sulfate concentration of 10.0 mM is included

pH of approximately 6.5 and with but 2 to 3 mgm ammonia nitrogen per 100 cc. A considerable amount of albumin was present, and the sediment was composed chiefly of granular casts and white blood cells. There were occasional hyaline casts. The Mosenthal test showed fixation of the specific gravity between 1.001 and 1.004. The concentration of non-protein nitrogen was never more than 240 mgm per cent. The concentration of chloride varied between 53 mgm and 99.5 mgm per cent NaCl. The phenolsulphonephthalein output was 19 per cent in 2 hours.

Polydipsia remained marked and all urine was as described above. Intramuscular injection of pituitrin had no effect on the concentration of the urine. With a high caloric diet, largely milk, she gained weight rapidly. Because of the diminished CO<sub>2</sub> content of the blood (see table 2), large amounts of orange juice, as an additional source of alkali, were given.

*Case 32* Woodrow W. Age, 9 years. Diagnosis Acute hemorrhagic nephritis when first seen which progressed into fatal chronic nephritis.

*Case 33* Davis B. Age, 13 years. Findings were those of chronic nephritis with hypertension (blood pressure 210/160) and myocardial damage.

*Case 34* Margaret Q. Age, 12 years. Diagnosis chronic nephritis with edema and hypertension.

*Cases 35 and 36* These cases were male adults showing evidence of renal insufficiency associated with prostatic hypertrophy. They are included because of the rather complete blood data which we were able to obtain from them and because they seemed in many respects like the children studied with marked renal insufficiency.

#### *Cases of subacute and chronic glomerular nephritis*

When acute glomerular nephritis is not completely recovered from, fibrous tissue replacement of kidney substance involving chiefly the glomeruli results. Autopsy of cases of severe chronic nephritis with evidence of marked renal insufficiency frequently shows very little normal secreting tissue remaining. It is, therefore, natural to assume that the chemical blood picture of severe chronic nephritis is the result of inadequate urinary secretion. It did not seem correct to us, however, to look upon non-protein nitrogen increase in the blood as conclusive evidence of renal insufficiency in cases of acute glomerular nephritis, and the data from the following cases of subacute and chronic nephritis make us feel that non-protein nitrogen increase in

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the blood has the same significance that it has in acute nephritis. In subacute or chronic nephritis, exacerbation of infection which provokes vomiting, diarrhea, or edema may have the same marked effect in lowering the electrolyte content of the blood and raising the non-protein nitrogen that it has in acute nephritis. In the absence of acute infection, however, the same result may occur more gradually, because of faulty urinary secretion which permits electrolyte to be lost from the blood.

*Results of acute infection in sub-acute or chronic nephritis*

When a severe exacerbation of infection in the form of paranasal sinusitis and septicemia by a hemolytic streptococcus occurred in case 24, on April 8, 1925, there followed a sudden appreciable reduction in concentration of serum chloride and bicarbonate (table 2, chart 2). If our single determination was correct, protein also suffered a transient but marked fall in concentration.<sup>1</sup> At the same time, edema appeared. Even in the absence of lactic acid and total base determinations, it seems certain that, as calculated, the osmotic pressure due to electrolyte suddenly diminished to a very marked degree, as calculated from 264 mM osmolar to 204 mM, a diminution of 22.8 per cent. Coincident with the fall in  $\text{BCl}$  and  $\text{BHCO}_3$ , non-protein nitrogen and phosphate increased in the blood, so that the total calculated osmolar concentration dropped somewhat less (17 per cent) than that of the electrolyte alone. On April 14, although the osmolar concentration of electrolyte was still much reduced, the total theoretical osmolar concentration was slightly higher than normal, due largely to increase in non-protein nitrogen. Edema had disappeared by this time. During the next few days, when the total osmolar concentration exceeded slightly the normal,<sup>2</sup> the reverse of edema, desiccation, was noted. Gradually, however, electrolyte

<sup>1</sup> The low plasma protein value on April 9th, however, is questionable, since determinations a short time previously and subsequently agreed well with each other and were both considerably higher than the value in question.

<sup>2</sup> As in case 21, the theoretical osmotic pressure was probably greater than the actual value when the non-protein nitrogen reached a very high level. In all probability, the non-protein nitrogen did not overcompensate osmotically for loss of electrolyte as much as our calculation would indicate.

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found to be the equivalent of 10 mM univalent base. We are inclined to believe, therefore, that in other instances in which undetermined acid seemed unusually large, as for instance cases 26, 28, 30, and 36, sulfuric acid was in all probability chiefly responsible.

In different types of nephritis, Straub studied the blood from an acid-base viewpoint by determining individually the base ions, Na, K, and Ca and the principle acid ions,  $\text{Cl}'$  and  $\text{HCO}_3'$ . He did not determine phosphoric, sulfuric, or lactic acid, and did not attempt to calculate the base-binding capacity of the protein. He did, however, besides determining the non-protein nitrogen, determine the actual freezing point and the electrical conductivity of the serum. He frequently found, as did later Bulger and Peters and ourselves, considerable variations in  $\text{Cl}'$  and  $\text{HCO}_3'$  ions, usually but not always in opposite directions. Total base ( $\text{Na} + \text{K} + \text{Ca}$ ) he found sometimes normal, but occasionally below or above normal. He also occasionally found an unusual excess of "total" base over the sum of  $\text{Cl}'$  and  $\text{HCO}_3'$  ions. This difference in some cases he did not believe due to phosphoric, sulfuric or proteic acid, but to some unknown pathological acid. This type of substance, together with a theoretical non-electrolyte (not non-protein nitrogen) constituted what he termed "molest," that is, the difference between the calculated and the observed osmotic pressure in millimoles.

Recalculating his most complete data as we <sup>our</sup> <sup>what</sup> <sup>calculated</sup> <sup>ours</sup>, we find the difference between "total" acid and <sup>base</sup> <sup>no</sup> <sup>greater</sup> than indicated by our data, and very little undetermined osmotically active substances except in one case (no 7 on July 23, 1923). In this instance, the total base found was 61 mM greater than the sum of the principal normal acids ( $\text{Cl}' + \text{HCO}_3' + \text{protein}'$ ). This is the only instance in which there was such a marked discrepancy between base and acid. In this case we should have expected very high values for phosphate and sulfate, together perhaps binding 25 to 30 mM univalent base. In addition, if marked circulatory failure had existed (as it very well might so shortly before death) lactic acid might have accounted for 10 to 15 mM more base. By accumulation of these three acids, therefore, 35 to 45 mM of the 61 might have been accounted for. In such an event, no very great amount of unusual acid needs to have been present. If we calculate the total

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ammonia for fixed base was noted, and cases 31, 32 and 36 also showed inability to practice base economy by excreting urine of maximum acidity

Such inability of the damaged kidney to practice base economy has been demonstrated experimentally by Begun and Munzer (11), Beckman (12) and Linder (13) in a more direct manner. After hydrochloric acid feeding in normal subjects and nephritics, a lesser excretion of ammonia and a greater excretion of fixed base was demonstrated in the urine of nephritics. In our case 28 there evidently had been severe renal insufficiency and "acidosis" for a considerable time and loss of the fixed base of the body seemed to have included also the calcium of the bones, producing a type of "renal" rickets.

The reason for the diminution of serum BCl in the absence of vomiting and edema seems also to lie in the faulty secretion of urine. Although our data on this point is not quantitative, it suggests at least that when there is a tendency towards secretion of large quantities of dilute urine, chloride may be present in the urine in considerable amount despite an abnormally low concentration in the serum. This is analogous to the chloride loss accompanying the polyuria of some cases of diabetes insipidus and diabetes mellitus. It is not inconceivable that such chloride loss in the urine, though relatively little, might eventually deplete the body if the chloride intake were restricted. Because of the inability of the kidney to practice base economy, such loss of chloride would also be attended by loss of fixed base.

It is of particular interest, however, that the osmotic pressure of the blood neither theoretically nor experimentally was found to be reduced, despite this reduction in  $\text{BHCO}_3$  and BCl. This was due to the fact that non-protein nitrogen was increased to a point sufficient to make up osmotically for the loss of electrolyte from the blood. This apparent compensation of a non-electrolyte for electrolyte in the maintenance of normal osmotic pressure in cases of chronic nephritis has also been noted in cases of marked vomiting due to pyloric or intestinal obstruction (2), in which electrolytes have been lost from the body and non-protein nitrogen retained. That such a mechanism may exist normally in some of the lower forms of life is suggested by the observation of MacCallum (14) that in the dogfish about one-third

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(1) The concentrations of the principal anions,  $\text{Cl}'$ ,  $\text{HCO}_3'$ , protein,  $\text{HPO}_4''$  and lactate, and the actual pH were determined

(2) Total base was determined directly, and from its value and the sum of the five principal acids determined the concentration of undetermined acid was obtained

(3) The principal non-electrolyte substances, non-protein nitrogen (urea) and glucose were determined

(4) The freezing point of the serum was determined and from it the total osmolar concentration of the serum was calculated

(5) A method of calculating the theoretical total osmolar concentration from the concentration of the principal individual solutes, electrolyte and non-electrolyte, was developed

In addition, the composition of the urine was studied to some extent, and after correlation of the observed changes in the chemical composition of the blood serum and urine with the clinical symptoms and findings, it was concluded that

(1) In *acute hemorrhagic nephritis*, marked changes in the chemical composition of the blood occur only when such symptoms as severe vomiting or diarrhea, edema or dehydration, or convulsions occur

(2) When these changes include a reduction of the total electrolyte content of the blood serum, urea is found increased to such an extent that no reduction in osmotic pressure occurs

(3) Such urea increase should be considered compensatory and not due to an inability of the kidney to excrete urea

(4) In *subacute* and *chronic* glomerular nephritis, acute infection causing similar symptoms results in similar changes

(5) In the absence of such symptoms, however, much the same changes occur, but more gradually, as the result of faulty urinary secretion which includes (a) failure to practice fixed base economy by substituting ammonia for the fixed base of the plasma salts when the acid radicals are excreted, and (b) a failure to secrete urine of normal maximum acidity, i e , free from  $\text{BHCO}_3$  and (c) a failure to retain  $\text{BCl}$  in the plasma, and (d) a failure to excrete sufficiently such acids as phosphoric and sulfuric

(6) The loss of plasma electrolyte due to such faulty urinary secretion is compensated for, osmotically, by retention of urea

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## METHOD OF STUDY

Interest in this study was prompted by the clinical observation of what seemed to be an abnormal degree of calcification in the peripheral arteries in older persons with polycythemia vera, as compared to that occurring in normal persons of like age

Fourteen typical cases of polycythemia vera were studied from this viewpoint. The spleen was enlarged in all. The number of erythrocytes, both absolute and relative, was greatly increased. The total blood volume, according to the dye method<sup>2</sup> (11), was greatly increased, owing to the absolute increase in the erythrocytes. The patients were hospitalized, three were given the low ionic diet of Keith, Smith and Whelan (11), the others were given the general hospital diet. Determinations were made in each case of the calcium content of the whole blood and serum before and following treatment with phenylhydrazine. The sodium, potassium, magnesium, phosphate, and the sodium chloride contents of the whole blood and serum were made in five cases before and after treatment with phenylhydrazine.

The hemoglobin was determined by the method of Osgood and Haskins. For serum sodium the method of Kramer and Tisdall (14), as modified by Whelan, was used. For calcium and potassium (13), the methods of Tisdall and Kramer were used. Magnesium was determined by the method of Bogert and Plass, which is a combination of Kramer and Tisdall's (15) magnesium method and of Briggs' phosphorus method, sodium sulphite was added to bring out the blue color, as directed by Briggs. In the whole blood a modification<sup>3</sup> of the method of Kramer and Tisdall (16) was used for the direct quantitative determination of sodium, potassium, calcium and

\* The hematocrit determinations were made by the dry oxalate method and a correction of 3 per cent in the cell volume was made for shrinkage.

<sup>3</sup> Ten cubic centimeters of blood, accurately measured in a pipette, was laked with about 25 cc. of water in a 100 cc. volumetric flask. From 10 to 15 cc. of 20 per cent trichloroacetic acid was added to complete the precipitation of the proteins. After the contents had been made up to volume with water, and filtered, 50 cc. of the filtrate was evaporated to dryness. The method of Kerr was employed in the removal of the trichloroacetic acid. After the aliquot had been evaporated to dryness again, the residue was dissolved in 0.2 N hydrochloric acid, transferred to a 10 cc. volumetric flask and made up to volume.

## METHOD OF STUDY

Interest in this study was prompted by the clinical observation of what seemed to be an abnormal degree of calcification in the peripheral arteries in older persons with polycythemia vera, as compared to that occurring in normal persons of like age

Fourteen typical cases of polycythemia vera were studied from this viewpoint. The spleen was enlarged in all. The number of erythrocytes, both absolute and relative, was greatly increased. The total blood volume, according to the dye method<sup>2</sup> (11), was greatly increased, owing to the absolute increase in the erythrocytes. The patients were hospitalized, three were given the low ionic diet of Keith, Smith and Whelan (11), the others were given the general hospital diet. Determinations were made in each case of the calcium content of the whole blood and serum before and following treatment with phenylhydrazine. The sodium, potassium, magnesium, phosphate, and the sodium chloride contents of the whole blood and serum were made in five cases before and after treatment with phenylhydrazine.

The hemoglobin was determined by the method of Osgood and Haskins. For serum sodium the method of Kramer and Tisdall (14), as modified by Whelan, was used. For calcium and potassium (13), the methods of Tisdall and Kramer were used. Magnesium was determined by the method of Bogert and Plass, which is a combination of Kramer and Tisdall's (15) magnesium method and of Briggs' phosphorus method, sodium sulphite was added to bring out the blue color, as directed by Briggs. In the whole blood a modification<sup>3</sup> of the method of Kramer and Tisdall (16) was used for the direct quantitative determination of sodium, potassium, calcium and

\* The hematocrit determinations were made by the dry ovalate method and a correction of 3 per cent in the cell volume was made for shrinkage.

<sup>3</sup> Ten cubic centimeters of blood, accurately measured in a pipette, was laked with about 25 cc of water in a 100 cc. volumetric flask. From 10 to 15 cc of 20 per cent trichloroacetic acid was added to complete the precipitation of the proteins. After the contents had been made up to volume with water, and filtered, 50 cc of the filtrate was evaporated to dryness. The method of Kerr was employed in the removal of the trichloroacetic acid. After the aliquot had been evaporated to dryness again, the residue was dissolved in 0.2 N hydrochloric acid, transferred to a 10 cc volumetric flask and made up to volume.

magnesium in small amounts of blood Smith's method was used for chloride determinations in serum and whole blood The serum protein was determined by the refractometric method

TABLE 3

*Polycythemia vera—studies on the calcium content of the blood and serum before and during treatment with phenylhydrazine*

| Case | Age | Sex               | Date | Hemoglobin     |           | Erythrocytes | Cells by the hematocrit | Blood volume |          | Plasma volume |          | Calcium            |       |                    |       |  |  |
|------|-----|-------------------|------|----------------|-----------|--------------|-------------------------|--------------|----------|---------------|----------|--------------------|-------|--------------------|-------|--|--|
|      |     |                   |      | grams per cent | mil lions |              |                         | Total        | Per kilo | Total         | Per kilo | Whole blood        |       | Serum              |       |  |  |
|      |     |                   |      |                |           |              |                         |              |          |               |          | Concen-<br>tration | Total | Concen-<br>tration | Total |  |  |
|      |     |                   |      |                |           |              |                         |              |          |               |          |                    |       |                    |       |  |  |
|      |     |                   |      |                |           |              |                         |              |          |               |          |                    |       |                    |       |  |  |
|      |     |                   |      |                |           |              |                         |              |          |               |          |                    |       |                    |       |  |  |
| 164  | M   | November 14, 1925 | 23 0 | 5 76           | 60        | 8,580        | 136                     | 3,430        | 54       | 5 2           | 445      | 12 6               | 432   |                    |       |  |  |
|      |     | December 7, 1925  | 12 8 | 2 99           | 35        | 4,730        | 75                      | 3,070        | 48       | 7 4           | 350      | 13 1               | 402   |                    |       |  |  |
| 255  | M   | December 5, 1926  | 26 0 | 7 00           | 75        | 14,700       | 180                     | 3,670        | 46       | 3 4           | 504      | 14 3               | 524   |                    |       |  |  |
|      |     | January 4, 1926   | 12 2 | 2 82           | 24        | 5,650        | 75                      | 4,290        | 57       | 7 5           | 424      | 10 1               | 433   |                    |       |  |  |
| 350  | M   | January 11, 1926  | 25 0 | 8 18           | 76        | 14,250       | 205                     | 3,420        | 49       | 4 0           | 574      | 17 3               | 591   |                    |       |  |  |
|      |     | February 4, 1926  | 15 2 | 4 51           | 38        | 6,450        | 104                     | 4,000        | 64       | 10 0          | 645      | 12 6               | 504   |                    |       |  |  |
| 462  | M   | January 28, 1925  | 21 4 | 5 70           | 65        | 9,900        | 173                     | 3,460        | 60       |               |          | 15 2               | 526   |                    |       |  |  |
|      |     | February 12, 1925 | 12 2 | 4 62           | 40        | 6,510        | 116                     | 3,910        | 70       |               |          | 9 3                | 364   |                    |       |  |  |
| 556  | M   | April 28, 1925    | 23 4 | 7 24           | 70        | 11,110       | 173                     | 3,330        | 52       |               |          | 15 8               | 526   |                    |       |  |  |
|      |     | May 6, 1925       | 20 8 | 4 97           | 60        | 8,760        | 136                     | 3,500        | 55       |               |          | 11 9               | 416   |                    |       |  |  |
|      |     | May 15, 1925      | 12 5 | 3 28           | 37        | 5,055        | 81                      | 3,185        | 51       |               |          | 10 6               | 336   |                    |       |  |  |
| 625  | M   | January 2, 1928   | 24 5 | 7 01           | 60        | 11,100       | 203                     | 3,330        | 61       | 5 8           | 679      | 18 1               | 602   |                    |       |  |  |
|      |     | January 21, 1928  | 18 1 | 5 68           | 53        | 7,660        | 150                     | 3,600        | 76       | 5 7           | 440      | 11 5               | 415   |                    |       |  |  |
| 739  | M   | January 18, 1928  | 27 3 | 7 60           | 76        | 17,250       | 223                     | 4,140        | 53       | 3 5           | 610      | 12 9               | 534   |                    |       |  |  |
|      |     | February 13, 1928 | 24 0 | 7 56           | 68        | 13,750       | 183                     | 4,400        | 59       | 3 8           | 519      | 9 8                | 431   |                    |       |  |  |
| 866  | F   | October 4, 1927   | 27 2 | 7 23           | 70        | 9,725        | 191                     | 2,925        | 58       | 5 0           | 488      | 12 9               | 387   |                    |       |  |  |
|      |     | November 10, 1927 | 15 3 | 4 24           | 47        | 5,565        | 114                     | 2,950        | 60       | 6 1           | 340      | 11 4               | 336   |                    |       |  |  |

All determinations were carried out in duplicate on fasting blood, and in several cases the direct method was checked by the trichloroacetic acid technic of Kramer and Tisdall (16) Control deter-

magnesium in small amounts of blood Smith's method was used for chloride determinations in serum and whole blood The serum protein was determined by the refractometric method

TABLE 3

*Polycythemia vera—studies on the calcium content of the blood and serum before and during treatment with phenylhydrazine*

| Case | Age | Sex   | Date                 | Hemoglobin           |                | Erythrocytes             | Cells by the hematocrit | Blood volume            |                | Plasma volume |            | Calcium              |                    |       |                    |       |
|------|-----|---|----------------------|----------------------|----------------|--------------------------|-------------------------|-------------------------|----------------|---------------|------------|----------------------|--------------------|-------|--------------------|-------|
|      |     |   |                      | grams per cent       | mil lions      |                          |                         | per cent                | Total          | Per kilo      | Total      | Per kilo             | Whole blood        |       | Serum              |       |
|      |     |   |                      |                      |                |                          |                         |                         |                |               |            |                      | Concen-<br>tration | Total | Concen-<br>tration | Total |
|      |     |   |                      |                      |                |                          |                         |                         |                |               |            |                      |                    |       |                    |       |
| 164  | M   | November 14, 1925<br>December 7, 1925         | 23 0<br>12 8         | 5 76<br>2 99         | 60<br>35       | 8,580<br>4,730           | 136<br>75               | 3,430<br>3,070          | 54<br>48       | 5 2<br>7 4    | 445<br>350 | 12 6<br>13 1         | 432<br>402         |       |                    |       |
| 255  | M   | December 5, 1926<br>January 4, 1926           | 26 0<br>12 2         | 7 00<br>2 82         | 75<br>24       | 14,700<br>5,650          | 180<br>75               | 3,670<br>4,290          | 46<br>57       | 3 4<br>7 5    | 504<br>424 | 14 3<br>10 1         | 524<br>433         |       |                    |       |
| 350  | M   | January 11, 1926<br>February 4, 1926          | 25 0<br>15 2         | 8 18<br>4 51         | 76<br>38       | 14,250<br>6,450          | 205<br>104              | 3,420<br>4,000          | 49<br>64       | 4 0<br>10 0   | 574<br>645 | 17 3<br>12 6         | 591<br>504         |       |                    |       |
| 462  | M   | January 28, 1925<br>February 12, 1925         | 21 4<br>12 2         | 5 70<br>4 62         | 65<br>40       | 9,900<br>6,510           | 173<br>116              | 3,460<br>3,910          | 60<br>70       |               |            | 15 2<br>9 3          | 526<br>364         |       |                    |       |
| 556  | M   | April 28, 1925<br>May 6, 1925<br>May 15, 1925 | 23 4<br>20 8<br>12 5 | 7 24<br>4 97<br>3 28 | 70<br>60<br>37 | 11,110<br>8,760<br>5,055 | 173<br>136<br>81        | 3,330<br>3,500<br>3,185 | 52<br>55<br>51 |               |            | 15 8<br>11 9<br>10 6 | 526<br>416<br>336  |       |                    |       |
| 625  | M   | January 2, 1928<br>January 21, 1928           | 24 5<br>18 1         | 5 01<br>5 68         | 60<br>53       | 11,100<br>7,660          | 203<br>150              | 3,330<br>3,600          | 61<br>76       | 5 8<br>5 7    | 679<br>440 | 18 1<br>11 5         | 602<br>415         |       |                    |       |
| 739  | M   | January 18, 1928<br>February 13, 1928         | 27 3<br>24 0         | 7 60<br>7 56         | 76<br>68       | 17,250<br>13,750         | 223<br>183              | 4,140<br>4,400          | 53<br>59       | 3 5<br>3 8    | 610<br>519 | 12 9<br>9 8          | 534<br>431         |       |                    |       |
| 866  | F   | October 4, 1927<br>November 10, 1927          | 27 2<br>15 3         | 7 23<br>4 24         | 70<br>47       | 9,725<br>5,565           | 191<br>114              | 2,925<br>2,950          | 58<br>60       | 5 0<br>6 1    | 488<br>340 | 12 9<br>11 4         | 387<br>336         |       |                    |       |

All determinations were carried out in duplicate on fasting blood, and in several cases the direct method was checked by the trichloroacetic acid technic of Kramer and Tisdall (16) Control deter-

TABLE 4  
*Polycythemia vera—Studies on the mineral substances of the blood before and during treatment with phenylhydrazine*

| Case | Age | Sex | Date  | Hemoglobin              |                         | Erythrocytes   |                          | Cells by the hematocrit |                   | Blood volume   |                   | Plasma volume |          | Sodium       |                   | Potassium         |                      | Magnesium  |              | Phosphate         |            | Calcium    |       | Sodium chloride |       |       |
|------|-----|-----|---|-------------------------|-------------------------|----------------|--------------------------|-------------------------|-------------------|----------------|-------------------|---------------|----------|--------------|-------------------|-------------------|----------------------|------------|--------------|-------------------|------------|------------|-------|-----------------|-------|-------|
|      |     |     |   | gms per cent            | mil lions               | per cent       | per cent                 | Per kilo                | cc                | Per kilo       | cc                | Serum         | Blood    | Serum        | Blood             | Serum             | Blood                | Serum      | Serum        | Blood             | Serum      | Serum      | Blood | Serum           | Serum | Blood |
|      |     |     |   |                         |                         |                |                          |                         |                   |                |                   |               |          |              |                   |                   |                      |            |              |                   |            |            |       |                 |       |       |
| 1    | 64  | M   | November 14, 1925<br>December 7, 1925         | 23.05<br>12.82          | 76.00<br>99.35          | 60<br>35       | 8,580<br>4,730           | 136.3<br>75.2           | 430<br>2,070      | 54<br>48       | 325<br>346        | 160<br>224    | 20<br>19 | 1270<br>7157 | 2.2<br>2.9        | 2.4<br>2.3        | 2.7<br>2.7           | 2.1<br>4.5 | 12.6<br>13.1 | 5.2<br>7.4        | 565<br>525 | 305        |       |                 |       |       |
| 2    | 55  | M   | December 5, 1926<br>January 1, 1926           | 26.07<br>12.22          | 70.00<br>82.24          | 75<br>24       | 14,700<br>5,650          | 180.3<br>75.4           | 670<br>290        | 46<br>57       | 425<br>340        | 194<br>114    | 35<br>19 | 0270<br>4135 | 3.7<br>3.2        | 6.7<br>5.0        | 2.7<br>2.5           | 2.6<br>2.8 | 14.3<br>10.1 | 3.4<br>7.5        | 660        | 580        |       |                 |       |       |
| 3    | 50  | M   | January 11, 1926<br>February 4, 1926          | 25.08<br>15.24          | 18.76<br>51.38          | 76<br>38       | 14,250<br>6,450          | 205.3<br>104.4          | 420<br>000        | 49<br>64       | 518               | 158           | 50       | 4280         | 3.1               | 2.7               | 2.1                  | 3.2        | 17.3<br>12.6 | 4.0<br>5.3        | 657<br>585 | 420<br>520 |       |                 |       |       |
| 4    | 62  | M   | January 28, 1925<br>February 12, 1925         | 21.45<br>12.24          | 57.06<br>62.40          | 65<br>40       | 9,900<br>6,510           | 173.3<br>116.3          | 460<br>910        | 60<br>70       | 420<br>337        | 28<br>21      | 0        |              | 5.0<br>2.8        | 3.9<br>3.2        | 15.2<br>9.3          |            |              |                   |            |            |       |                 |       |       |
| 5    | 56  | M   | April 28, 1925<br>May 6, 1925<br>May 15, 1925 | 23.47<br>20.84<br>12.53 | 72.24<br>97.60<br>28.37 | 70<br>60<br>37 | 11,110<br>8,760<br>5,055 | 173.3<br>136.3<br>81.3  | 330<br>500<br>185 | 52<br>55<br>51 | 394<br>401<br>358 |               |          |              | 4.6<br>1.8<br>2.5 | 2.6<br>2.4<br>2.9 | 15.8<br>11.9<br>10.6 |            |              | 610<br>570<br>580 |            |            |       |                 |       |       |

TABLE 4  
*Polycythemia vera—Studies on the mineral substances of the blood before and during treatment with phenylhydrazine*

| Case | Age | Sex | Date                           | Hemoglobin                          |                      | Erythrocytes<br>mil<br>per<br>cmm | Cells by the<br>hematocrit | Blood<br>volume          |                  | Plasma<br>volume        |                | Sodium                           |                                  | Potassium                        |                                  | Magnesium                        |                                  | Phosphate                        |                                  | Calcium                          |                                  | Sodium<br>chloride               |                                  |
|------|-----|-----|--------------------------------|-------------------------------------|----------------------|-----------------------------------|----------------------------|--------------------------|------------------|-------------------------|----------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|      |     |     |                                | gms<br>per<br>cent                  | gms<br>per<br>cent   |                                   |                            | Total<br>cc              | Per kilo         | Total<br>cc             | Per kilo       | Serum<br>mgm<br>per<br>100<br>cc | Blood<br>mgm<br>per<br>100<br>cc | Serum<br>mgm<br>per<br>100<br>cc | Blood<br>mgm<br>per<br>100<br>cc | Serum<br>mgm<br>per<br>100<br>cc | Blood<br>mgm<br>per<br>100<br>cc | Serum<br>mgm<br>per<br>100<br>cc | Blood<br>mgm<br>per<br>100<br>cc | Serum<br>mgm<br>per<br>100<br>cc | Blood<br>mgm<br>per<br>100<br>cc | Serum<br>mgm<br>per<br>100<br>cc | Blood<br>mgm<br>per<br>100<br>cc |
| 1    | 64  | M   | November 14,<br>December 7,    | 1925 23.0<br>1925 12.8              | 23.0<br>12.9         | 576<br>99                         | 60<br>35                   | 8,580<br>4,730           | 136<br>75        | 3,430<br>2,070          | 54<br>48       | 325<br>346                       | 160<br>224                       | 20<br>19                         | 1270<br>7157                     | 22<br>29                         | 24<br>23                         | 27<br>27                         | 212<br>45                        | 126<br>131                       | 52<br>74                         | 565<br>525                       | 305<br>525                       |
| 2    | 55  | M   | December 5,<br>January 1,      | 1926 26.0<br>1926 12.2              | 26.0<br>12.8         | 700<br>82                         | 75<br>24                   | 14,700<br>5,650          | 180<br>75        | 3,670<br>4,290          | 46<br>57       | 425<br>340                       | 194<br>114                       | 35<br>19                         | 0270<br>4135                     | 37<br>32                         | 67<br>50                         | 27<br>25                         | 26<br>8                          | 143<br>101                       | 34<br>75                         | 660<br>580                       |                                  |
| 3    | 50  | M   | January 11,<br>February 4,     | 1926 25.0<br>1926 15.2              | 25.0<br>15.4         | 18<br>51                          | 76<br>38                   | 14,250<br>6,450          | 205<br>104       | 3,420<br>4,000          | 49<br>64       | 518                              | 158                              | 50                               | 4280                             | 31<br>22                         | 27<br>78                         | 21<br>89                         | 21<br>33                         | 217<br>28                        | 340<br>126                       | 657<br>585                       | 420<br>520                       |
| 4    | 62  | M   | January 28,<br>February 12,    | 1925 21.4<br>1925 12.2              | 21.4<br>12.6         | 70<br>62                          | 65<br>40                   | 9,900<br>6,510           | 173<br>116       | 3,460<br>3,910          | 60<br>70       | 420<br>337                       |                                  | 28<br>21                         | 0<br>0                           |                                  | 5<br>2                           | 3<br>3                           | 9<br>2                           | 15<br>9                          | 2<br>3                           |                                  |                                  |
| 5    | 56  | M   | April 28,<br>May 6,<br>May 15, | 1925 23.4<br>1925 20.8<br>1925 12.5 | 23.4<br>20.8<br>12.3 | 24<br>97<br>28                    | 70<br>60<br>37             | 11,110<br>8,760<br>5,055 | 173<br>136<br>81 | 3,330<br>3,500<br>3,185 | 52<br>55<br>51 | 394<br>401<br>358                |                                  |                                  |                                  |                                  | 4<br>1<br>2                      | 6<br>4<br>9                      | 2<br>2<br>10                     | 15<br>11<br>10                   | 8<br>9<br>6                      | 610<br>570<br>580                |                                  |



the assumption that the increased calcium is related to an increase in the serum protein with variation in the colloid-calcium combination. In two cases studied, slight increases in the serum proteins were found. Studies have not been carried out in our cases to determine whether the diffusible or the nondiffusible fractions, or both, are increased. Methods for the study of this question are being developed.

The most logical explanation for the hypercalcemia in this disease is that it is related in some manner to the great increase in the absolute number of erythrocytes, since a definite decrease in the calcium levels in the serum follow the reduction in the number of erythrocytes. Apparently a relative increase in the ratio of corpuscles to plasma is not accompanied by an increase in the calcium, since normal values were obtained in a case of relative polycythemia vera due to dehydration, in which there were 60 per cent of cells by the hematocrit. The absence of an increase in the serum calcium in relative polycythemia vera is in accord with the work of Van Slyke. He showed that change does not occur in the inorganic ratios with variations in the relative amount of cells or plasma, since the concentration of the inorganic substances remains the same.

It could be assumed that the increased concentration of calcium represents an effort to maintain the normal inorganic ratios in the blood. Against this premise is the presence of increased values for serum calcium associated with normal values for serum potassium. There is no explanation for the increase in serum potassium in the cases in which it is observed, since it has been shown that this electrolyte does not pass through the cell membrane.

The decrease in the percentage concentration of calcium following treatment is due to a decrease in the total calcium of the serum and to dilution from the increased amount of plasma. As an example (case 2, table 3), the total serum calcium decreased 17 per cent, the actual plasma volume increased 17 per cent, and the concentration of serum calcium decreased from 17.3 to 12.6 mgm (30 per cent). Approximately half of the percentage change in calcium was related to the variation in the plasma. Either the concentration of calcium in the tissue fluid was low or an abnormal excretion of calcium occurred during hemolysis. Data regarding the excretion of calcium during the period of blood destruction are lacking.

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It could be assumed that the increased concentration of calcium represents an effort to maintain the normal inorganic ratios in the blood. Against this premise is the presence of increased values for serum calcium associated with normal values for serum potassium. There is no explanation for the increase in serum potassium in the cases in which it is observed, since it has been shown that this electrolyte does not pass through the cell membrane.

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## SUMMARY AND CONCLUSIONS

Fourteen subjects presenting the classic picture of polycythemia vera showed an increase in the serum calcium above the accepted range of normal. The values in this substance ranged from 11.1 to 18.1 mgm for each 100 cc of serum. The average value was 14.3 mgm.

Following treatment with phenylhydrazine and destruction of corpuscles to approximately normal or even subnormal values, the percentage concentration of serum calcium decreased to levels slightly above normal.

The basis of the hypercalcemia is not known. It may represent a compensatory effort to maintain the inorganic ratios of the blood. Hypercalcemia in the human subject can be tolerated without grave disturbance to the organism. The susceptibility of patients with polycythemia vera to thrombosis and to high grades of calcification in the peripheral vessels in some cases of polycythemia vera may be late results of hypercalcemia.<sup>5</sup>

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<sup>5</sup>We have encountered three cases of mild polycythemia vera during the last three months with volumes of blood, 128, 131 and 140 cc for each kilogram, with serum calcium values of 10.6, 10.4 and 11.3 mgm respectively. These data indicate that there are cases of mild degrees of polycythemia vera in which hypercalcemia is probably not present at this stage.

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- 8 Hueper, Wilhelm, *Arch Path and Lab Med*, 1927, iii, 14. Metastatic Calcifications in the Organs of the Dog after Injections of Parathyroid Extract.

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<sup>5</sup> We have encountered three cases of mild polycythemia vera during the last three months with volumes of blood, 128, 131 and 140 cc for each kilogram, with serum calcium values of 10.6, 10.4 and 11.3 mgm respectively. These data indicate that there are cases of mild degrees of polycythemia vera in which hypercalcemia is probably not present at this stage.





these physiological constants at their normal levels shows that the respiratory function is, in fact, in fair working order. This statement must, however, be qualified, since the other chief function of the respiration—the supply of oxygen to the tissues—is impaired. No actual measurement of the oxygen tension in the tissues has been made, nor of the tension in the arterial blood of pneumonia patients. The oxygen content and capacity of the arterial blood is, however, readily measurable, and from these figures one can obtain an estimate of the efficiency of the respiratory mechanism.

It is probably not inaccurate to say that almost every case of pneumonia shows at some time a deficiency in the oxygen saturation of the arterial blood (2). The fact that there may be oxygen want and still no carbon dioxide retention or shift in the neutrality regulation of the blood is explicable on the basis of the different physical properties of  $O_2$  and  $CO_2$  and the different manner in which they combine with hemoglobin. This subject has been fully discussed by Haldane (3).

Lundsgaard and Van Slyke (4) have attempted to analyze the various factors which contribute to the presence of cyanosis. The origin of cyanosis in pneumonia, it seems safe to state, is respiratory rather than circulatory. It is, however, by no means clear why the blood is incompletely oxygenated in the lungs. Several explanations have been offered for this, viz., unequal expansion of the lungs (5), rapid and shallow breathing (6), diminished lung volume (7), intra-alveolar exudate (8), decreased oxygen diffusion resulting from toxic injury of alveolar walls (9), passage of blood through unaerated channels in the lung (10). It has, moreover, been shown experimentally that an increased rate of blood flow through the lungs may prevent the hemoglobin from taking up its normal load of oxygen (11). Whether this last actually plays a rôle in pneumonia is, to be sure, doubtful, but there seems little doubt that some or all of the other factors may combine to prevent the complete reoxygenation of the blood in its passage through the lungs. Plausible as these explanations may be, the actual proof of their influence and the proper weighting of their importance remains difficult, if not impossible. One can never know the true state of the parenchymatous and vascular lesion in the lung at the time of the arterial oxygen analysis. The relationship of these two must therefore remain a matter of inference and conjecture.

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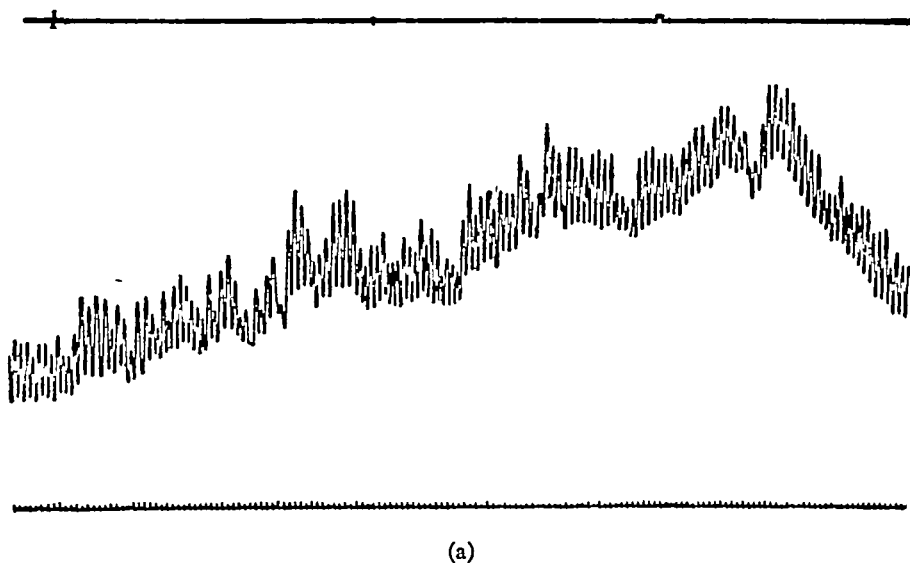


FIG 1 (a) PLETHYSMOGRAPHIC TRACING FROM CASE 10, MADE ON THE FOURTH DAY AFTER ONSET OF ILLNESS, (b) PLETHYSMOGRAPHIC TRACING FROM SAME PATIENT MADE DURING CONVALESCENCE, ON TWENTY-FIFTH DAY AFTER ONSET OF ILLNESS

The upper line was drawn by the work-adder signal lever. Interval between signal lever marks equals 12.34 liters. The lower line represents time in 2 second intervals.

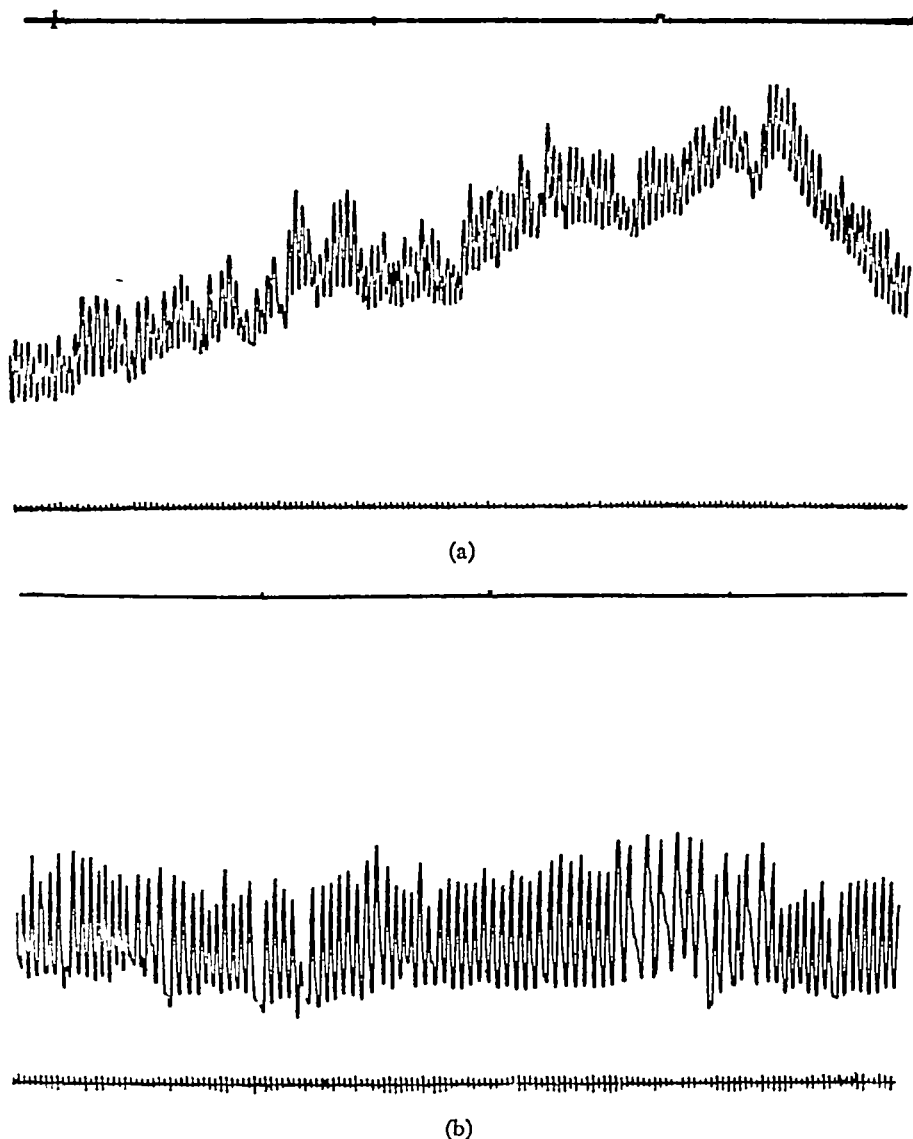


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TABLE 1

| History number | Care number | Observation number | Date              | Area of pulmonary involvement | Organism                           | Day after onset | Day of disease term malperature was not | Vital capacity | Minute volume | Tidal air | Respiratory rate | Duration of inspiration | Duration of expiration | Ratio Expiration/Inspiration | Temperature °F | Pulse rate | O <sub>2</sub> content | O <sub>2</sub> capacity | O <sub>2</sub> saturation | Remarks   |
|----------------|-------------|--------------------|-------------------|-------------------------------|------------------------------------|-----------------|---|----------------|---------------|-----------|------------------|-------------------------|------------------------|------------------------------|----------------|------------|------------------------|-------------------------|---------------------------|-----------|
| 6212           | 1           | 1                  | December 1, 1927  | I L I<br>R L I                | Group IV<br>St <sup>a</sup> aureus | 3               | 30                                      | 2 40           | 10 97         | 305       | 36               | 0 63                    | 0 98                   | 1 55                         | 104 0          | 120 11     | 35 16                  | 89 85                   | 0                         |           |
|                |             | 2                  | December 25, 1927 |                               |                                    | 27              |   | 3 98           | 7 74          | 537       | 14 4             | 1 40                    | 2 22                   | 1 59                         | 100 0          | 95 15      | 30 16                  | 23 94                   | 4                         | Recovered |
| 6213           | 2           | 1                  | December 17, 1927 | R M I                         | Type I                             | 4               | 9                                       |                | 13 35         | 417       | 32               | 0 81                    | 0 94                   | 1 16                         | 103 5          | 115 16     | 83 20                  | 58 81                   | 8                         |           |
|                |             | 2                  | January 1, 1928   | R I I                         |                                    | 22              |   | 2 73           | 5 89          | 420       | 14               | 1 19                    | 2 68                   | 2 25                         | 99 0           | 65 17      | 86 18                  | 95 94                   | 3                         |           |
|                |             | 3                  | January 19, 1928  |                               |                                    | 37              |   | 2 74           | 8 04          | 473       | 17               | 1 24                    | 2 18                   | 1 76                         | 98 6           |            | 85 18                  | 70 95                   | 5                         |           |
|                |             | 4                  | March 3, 1928     |                               |                                    | 81              |   | 3 67           | 6 17          | 472       | 14 2             | 1 38                    | 2 50                   | 1 81                         |                |            | 55 20                  | 22 96                   | 7                         | Recovered |
| 6216           | 3           | 1                  | January 5, 1928   | L U L<br>L L L                | Type III                           | 4               |   | 1 47           | 15 78         | 493       | 32               | 0 83                    | 0 91                   | 1 09                         | 103 0          | 116 13     | 26 16                  | 08 82                   | 5                         | Died      |
| 6217           | 1           | 1                  | January 6, 1928   | R U L<br>R M L<br>R L L       | Type III                           | 3               |   | 1 45           | 15 42         | 440       | 35               | 0 68                    | 1 02                   | 1 50                         | 104 0          | 120 14     | 35 17                  | 79 80                   | 7                         | Died      |
| 6259           | 5           | 1                  | January 11, 1928  | R L I                         | Type I                             | 4               | 14                                      | 1 62           | 9 38          | 375       | 25               | 0 91                    | 1 31                   | 1 44                         | 101 4          | 128 17     | 06 19                  | 24 88                   | 7                         |           |
|                |             | 2                  | February 10, 1928 |                               |                                    | 31              |   | 3 34           | 7 16          | 421       | 17               | 1 49                    | 2 40                   | 1 61                         | 99 0           | 84 17      | 12 13                  | 35 93                   | 4                         | Recovered |
| 6270           | 6           | 1                  | January 20, 1928  | I L I                         | Type IV                            | 4               | 4                                       | 0 67           | 6 12          | 282       | 21 7             | 0 95                    | 2 00                   | 2 10                         | 99 8           | 94 18      | 50 20                  | 10 92                   | 0                         |           |
|                |             | 2                  | January 27, 1928  |                               |                                    | 11              |   | 1 73           | 5 62          | 356       | 15 8             | 1 02                    | 2 36                   | 2 31                         | 98 6           | 70 19      | 17 20                  | 20 95                   | 3                         | Recovered |

TABLE 1

| H of patient | Case number | Obduction number | Date              | Area of pulmonary involvement | Organism   | Day after onset | Day of disease terminal | Vital capacity | Minute volume | Tidal air | Respiratory rate | Duration of inspiration | Ratio Expiration/Inspiration | Temperature | Pulse rate | O <sub>2</sub> content      | O <sub>2</sub> capacity     | O <sub>2</sub> saturation | Remarks   |
|--------------|-------------|------------------|-------------------|-------------------------------|------------|-----------------|-------------------------|----------------|---------------|-----------|------------------|-------------------------|------------------------------|-------------|------------|-----------------------------|-----------------------------|---------------------------|-----------|
|              |             |                  |                   |                               |            |                 |                         | liters         | liters        | cc        |                  | sec<br>onds             |                              | °           |            | vol<br>times<br>per<br>cent | vol<br>times<br>per<br>cent | per<br>cent               |           |
| 6212         | 1           | 1                | December 1, 1927  | I L I                         | Group IV   | 3               | 30                      | 2 40           | 10 97         | 305       | 36               | 0 63                    | 1 55                         | 104 0       | 120        | 11 35                       | 16 89                       | 85 0                      | Recovered |
|              |             |                  | December 25, 1927 | R L I                         | Str aureus | 27              |                         | 3 98           | 7 74          | 537       | 14 4             | 1 40                    | 2 22                         | 1 59        | 100 0      | 95 15                       | 30 16                       | 23 94                     |           |
| 6212         | 2           | 1                | December 17, 1927 | R M I                         | Type I     | 4               | 9                       |                | 13 35         | 417       | 32               | 0 81                    | 0 94                         | 1 16        | 103 5      | 115 16                      | 83 20                       | 58 81                     | Recovered |
|              |             |                  | January 1, 1928   | R I I                         |            | 22              |                         | 2 73           | 5 89          | 420       | 14               | 1 19                    | 2 68                         | 2 25        | 99 0       | 65 17                       | 86 18                       | 95 94                     |           |
|              |             |                  | January 19, 1928  |                               |            | 37              |                         | 2 74           | 8 04          | 473       | 17               | 1 24                    | 2 18                         | 1 76        | 98 6       | 17 85                       | 18 70                       | 95 5                      |           |
|              |             |                  | March 3, 1928     |                               |            | 81              |                         | 3 67           | 6 17          | 472       | 14 2             | 1 38                    | 2 50                         | 1 81        |            | 19 55                       | 20 22                       | 96 7                      |           |
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| 6217         | 1           | 1                | January 6, 1928   | R U L<br>R M L<br>R L L       | Type III   | 3               |                         | 1 45           | 15 42         | 440       | 35               | 0 68                    | 1 02                         | 1 50        | 104 0      | 120 14                      | 35 17                       | 79 80                     | Died      |
| 6259         | 5           | 1                | January 11, 1928  | R L I                         | Type I     | 4               | 14                      | 1 62           | 9 38          | 375       | 25               | 0 91                    | 1 31                         | 1 44        | 101 4      | 128 17                      | 06 19                       | 24 88                     | Recovered |
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| 6270         | 6           | 1                | January 20, 1928  | I L I                         | Type IV    | 4               | 4                       | 0 67           | 6 12          | 282       | 21 7             | 0 95                    | 2 00                         | 2 10        | 99 8       | 94 18                       | 50 20                       | 10 92                     | Recovered |
|              |             |                  | January 27, 1928  |                               |            | 11              |                         | 1 73           | 5 62          | 356       | 15 8             | 1 02                    | 2 36                         | 2 31        | 98 6       | 70 19                       | 17 20                       | 20 95                     |           |

TABLE 1—Continued

| History number | Case number | Observation number | Date           | Area of pulmonary involvement    | Organism         | Day after onset | Day of disease terminated | Vital capacity | Minute volume | Tidal air | Respiratory rate | Duration of inspiration | Ratio<br>Expiration<br>Inspiration | Temperature | Pulse rate | O <sub>2</sub> content | O <sub>2</sub> capacity | O <sub>2</sub> saturation | Remarks                         |
|----------------|-------------|--------------------|----------------|----------------------------------|------------------|-----------------|---------------------------|----------------|---------------|-----------|------------------|-------------------------|------------------------------------|-------------|------------|------------------------|-------------------------|---------------------------|---------------------------------|
| 6410           | 15          | 1                  | April 17, 1928 | R M L<br>R L L<br>L L L          | Group IV         | 2               |                           |                | 12 23         | 266       | 46               | 0 63                    | 0 74                               | 1 17        | 102 4      | 144 12 48              | 18 97                   | 65 8                      | Died                            |
| 6411           | 16          | 1                  | April 20, 1928 | L L L<br>R U L<br>R L L          | Group IV         | 4               |                           |                | 13 18         | 376       | 35               | 0 81                    | 0 78                               | 0 96        | 102 8      | 112 18 05              | 20 60                   | 87 7                      | Died                            |
| 6439           | 17          | 1                  | May 29, 1928   | L U L<br>L L L<br>R L L<br>R M L | Group IV<br>Tbc. | 23              |                           | 6 57           | 10 67         | 331       | 32 2             | 0 85                    | 1 04                               | 1 22        | 102 0      | 115 13 05              | 14 18                   | 92 1                      | Discharged to convalescent home |

TABLE 1—Continued

| History number | Case number | Observation number | Date           | Area of pulmonary involvement    | Organism         | Day after onset | Day of disease when temperature was normal | Vital capacity<br>liters | Minute volume<br>liters | Tidal air<br>cc | Respiratory rate | Duration of inspiration<br>sec | Ratio<br>Expiration<br>Inspiration | Temperature<br>°C | Pulse rate | O <sub>2</sub> content<br>vol<br>umes<br>per<br>cent | O <sub>2</sub> capacity<br>vol<br>umes<br>per<br>cent | O <sub>2</sub> saturation | Remarks                         |
|----------------|-------------|--------------------|----------------|----------------------------------|------------------|-----------------|--|--------------------------|-------------------------|-----------------|------------------|--------------------------------|------------------------------------|-------------------|------------|--|---|---------------------------|---------------------------------|
| 6110           | 15          | 1                  | April 17, 1928 | R M L<br>R L L<br>L L L          | Group IV         | 2               |  | 12 23                    | 266                     | 46              | 0 63             | 0 74                           | 1 17                               | 102 4             | 144        | 12 48  | 18 97   | 65 8                      | Died                            |
| 6111           | 16          | 1                  | April 20, 1928 | L L L<br>R U L<br>R L L          | Group IV         | 4               |  | 13 18                    | 376                     | 35              | 0 81             | 0 78                           | 0 96                               | 102 8             | 112        | 18 05  | 20 60   | 87 7                      | Died                            |
| 6130           | 17          | 1                  | May 29, 1928   | L U L<br>L L L<br>R L L<br>R M L | Group IV<br>Tbc. | 23              |  | 6 57                     | 10 67                   | 331             | 32 2             | 0 85                           | 1 04                               | 1 22              | 102 0      | 115 13   | 05 14 18  | 92 1                      | Discharged to convalescent home |

*The effect of oxygen inhalation on the respiratory rate and depth*

Three patients of the series were studied both while breathing room air and again with the plethysmograph placed inside the oxygen chamber while the patients were permitted to inhale a 40 to 44 per cent oxygen mixture. It was hoped to glean from this procedure further information as to the relative interdependence of rapid and shallow breathing and anoxemia.

*Case 14* J. G., male, age 23. Hospital No. 6357. Diagnosis: Lobar pneumonia, empyema, thoracotomy.

*Present illness* For 2 days the patient had complained of pain in his left side and chills. He was admitted on March 18, 1928.

*Physical examination* Severe pain was obvious. There was slight cyanosis of nail beds and face. The temperature was  $105.4^{\circ}\text{F}$ , pulse 132, respirations 60. The leucocyte count was 34,700. Examination of the chest showed slight dullness over angle of scapula. Below this point breath sounds were suppressed.

*X-ray examination* Diffuse opacity from left apex to base, most marked at base.

*Bacteriological examination* Group IV pneumococcus and hemolytic streptococcus were recovered from sputum. Blood culture sterile.

*Course* Plethysmographic tracings were made before and during oxygen administration. This was accomplished by placing the plethysmograph inside the oxygen chamber. The first plethysmographic tracing was made March 19, a day after admission. The temperature was then  $103.2^{\circ}\text{F}$ , pulse 128. The respiratory rate was 44, tidal air 255 cc, and minute volume 11.20 liters. The expiratory-inspiratory ratio was 0.96. The arterial blood analysis showed a percentage saturation of 81.7, with the oxygen content and capacity 16.15 and 19.79 vols per cent, respectively. After these observations had been made the oxygen concentration in the chamber was raised to 44.5 per cent. Two hours later a second series of plethysmographic observations were made. The respiratory rate was now 46.7, tidal air 228 cc, and minute volume 10.67 liters. The ratio of expiration to inspiration was now 1.34. Arterial saturation had increased to 94.4 per cent with an oxygen content of 20.12 vols per cent and capacity of 21.68 vols per cent.

*Comment on case 14*

The result of putting the patient in the chamber was to raise the  $\text{O}_2$  content of the arterial blood approximately 4 vols per cent and to increase the per cent saturation from 81.7 to 94.4. No slowing or deepening of respirations occurred. It may be assumed that the

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*Case 16* J M, male, age 32 Hospital No 6414 Diagnosis Lobar pneumonia, septicemia

*Present illness* The patient had been sick for 3 days, complaining of pain in the left chest, chills, cough, and expectoration of blood tinged sputum. He was brought to the hospital on April 19, 1928.

*Physical examination* There was slight cyanosis of nail beds. Temperature was 104°F, pulse 120, respirations 36. The leucocyte count was 14,000. The chest signs showed, from spine of left scapula to base posteriorly there was dullness to flatness, voice and breath sounds increased except at very base where they were diminished, bronchial breathing and occasional crepitant râle at angle of left scapula, dullness and occasional sub-crepitant râle at the right base.

*X-ray examination* Opacity of area occupied by left lower lobe, lower part of right upper lobe and right lower lobe.

*Bacteriological examination* Group IV pneumococcus was recovered from the sputum and blood.

*Course* On April 20 the patient was transferred to the oxygen chamber because he was growing more cyanotic and his breathing was becoming more difficult. Before oxygen was administered a *plethysmographic record* was made. His temperature was then 102.8°F, pulse 112. The respiratory rate was 35, tidal air 376 cc, and minute volume 13.18 liters. The *arterial blood oxygen content* was 18.05 vols per cent, with a capacity of 20.60 vols per cent, the saturation being 87.7 per cent.

Two and a half hours later, after the patient had been in an atmosphere of 39.5 per cent oxygen for 1½ hours, a *second plethysmographic tracing* was made. No significant change had occurred in any of the measurements. The respiratory rate was now 35.2, tidal air 372 cc, minute volume 13.08 liters. The arterial oxygen content and capacity had risen respectively to 18.54 and 20.80 vols per cent. The saturation was now 89.0 per cent. In spite of this slight increase the patient's color was obviously better and he said he felt better.

The next day the patient became rapidly worse and died on April 23. His blood culture was positive, there being more than 100 colonies to the cubic centimeter of blood.

#### *Comment on case 16*

The case is similar to the last one, a rapidly fatal pneumonia which did not respond to oxygen therapy either by a significant increase in the per cent saturation of arterial blood or by a slowing or deepening

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Relatively large values for the minute volume of pulmonary ventilation are found almost without exception during the acute stage of pneumonia, and become smaller during convalescence. This has been looked upon by some as of a compensatory nature. If so, the compensation is obviously inadequate with respect to the aeration of the blood in the lungs.

With regard to the vital capacity, its measurement is perhaps of not much significance except as an indication of pleuritic pain. The functional residual air studied by Binger and Brow (7) is of greater interest, and this we believe should be reinvestigated from the point of view of anoxemia.

#### SUMMARY AND CONCLUSIONS

- 1 By means of a specially designed body plethysmograph the respiratory movements have been studied in a group of patients suffering from acute pneumonia.

- 2 The oxygen content, capacity and per cent saturation have also been measured.

- 3 Observations have been made during the acute stage of the disease during convalescence, after morphine administration and oxygen inhalation.

- 4 Rapid and shallow breathing, and anoxemia are commonly associated phenomena.

- 5 No clear evidence can be adduced, however, that the anoxemia which occurs in lobar pneumonia is the result of rapid and shallow breathing, though in some cases extremely rapid and shallow breath-

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TABLE 1

Data showing effect of morphine on respiratory movements and oxygen saturation of arterial blood of patients suffering from pneumonia

| Case number | His case number | Date                | Dose of morphine | Respiratory rate | Temperature | Pulse | Area of pulmonary involvement | Tidal air | Minute volume | Duration of inspiration | Duration of expiration | Ratio inspiration to expiration | Oxygen content     | Oxygen capacity    | Per cent saturation | Remarks                            |
|-------------|-----------------|---------------------|------------------|------------------|-------------|-------|-------------------------------|-----------|---------------|-------------------------|------------------------|---------------------------------|--------------------|--------------------|---------------------|------------------------------------|
|             |                 |                     | mgm              |                  | F           |       |                               | cc        | liters        | sec onds                | sec onds               |                                 | vol times per cent | vol times per cent |                     |                                    |
| 16212       |                 | 1927<br>December 17 | 16               | 32 0*            | 103 5       | 115   | R M L<br>R I I                | 417 13    | 35 0          | 81 0                    | 94                     | 1 16                            | 16 83              | 20 58              | 81 8                | Severe pain                        |
|             |                 |                     |                  | 25 0             |             |       |                               | 438 10    | 96 1          | 06 1                    | 80                     | 1 70                            | 17 18              | 20 58              | 83 6                | Recovered                          |
| 26216       |                 | 1928<br>January 5   | 18               | 32 0             | 103 0       | 116   | I U L<br>I L L                | 493 15    | 78 0          | 83 0                    | 91                     | 1 07                            | 13 26              | 16 08              | 82 5                | Edema of lung<br>Pleural effusion  |
|             |                 |                     |                  | 30 5             |             |       |                               | 355 10    | 83 0          | 75 1                    | 31                     | 1 75                            | 10 86              | 16 74              | 64 9                | Treated in oxygen chamber,<br>died |
| 36217       |                 | January 6           | 10               | 35 0             | 104 0       | 120   | R U I<br>R M L<br>R I L       | 440 15    | 42 0          | 68 1                    | 02                     | 1 50                            | 14 35              | 17 79              | 80 7                | Respirations very labored          |
|             |                 |                     |                  | 34 5             |             |       |                               | 422 14    | 57 0          | 75 1                    | 03                     | 1 37                            |                    |                    |                     | Died                               |
| 16259       |                 | January 11          | 12               | 25 0<br>22 0     | 101 4       | 128   | R L I                         | 375 9     | 38 0          | 91 1                    | 31                     | 1 44                            | 17 06              | 19 24              | 88 7                | Pain Serum treatment               |
|             |                 |                     |                  |                  |             |       |                               | 357 7     | 86 0          | 99 1                    | 82                     | 1 84                            | 17 40              | 20 00              | 87 0                | Recovered                          |
| 56262       |                 | January 17          | 10               | 21 0<br>19 6     | 100 0       | 80    | R L L                         | 405 8     | 50 1          | 41 1                    | 71                     | 1 21                            | 16 69              | 18 41              | 90 7                | Not acutely ill                    |
|             |                 |                     |                  |                  |             |       |                               | 348 6     | 83 1          | 50 2                    | 12                     | 1 41                            | 17 06              | 18 42              | 92 6                | Recovered                          |
| 66264       |                 | January 16          | 12               | 40 0             | 103 0       | 108   | R U L<br>R L L                |           |               |                         |                        |                                 | 17 09              | 20 08              | 85 2                | Died                               |
|             |                 |                     |                  | 42 0             | 103 8       | 120   |                               |           |               |                         |                        |                                 | 16 86              | 20 05              | 84 1                |                                    |

TABLE 1  
Data showing effect of morphine on respiratory movements and oxygen saturation of arterial blood of patients suffering from pneumonia

| Case number | Date                | Dose of morphine<br>mgm | Respiratory rate | Temperature    | Pulse | Area of pulmonary involvement | Tidal air<br>cc | Minute volume<br>liters | Duration of inspiration<br>sec | Duration of expiration<br>sec | Ratio inspiration to expiration | Oxygen content<br>vol times per cent | Oxygen capacity<br>vol times per cent | Per cent saturation | Remarks   |
|-------------|---------------------|-------------------------|------------------|----------------|-------|-------------------------------|-----------------|-------------------------|--------------------------------|-------------------------------|---------------------------------|--------------------------------------|---------------------------------------|---------------------|---|
| 16232       | 1927<br>December 17 | 16                      | 32 0*            | 103 5          | 115   | R M L<br>R I I                | 417 13          | 350 81                  | 0 94                           | 1 16                          | 16 83                           | 20 58                                | 81 8                                  |                     | Severe pain   |
|             | 1928<br>January 5   |                         | 25 0             |                |       |                               | 438 10          | 96 1 06                 | 1 80                           | 1 70                          | 17 18                           | 20 58                                | 83 6                                  |                     | Recovered   |
| 26216       | January 5           | 18                      | 32 0             | 103 0          | 116   | I U L<br>I L L                | 493 15          | 78 0 83                 | 0 91                           | 1 07                          | 13 26                           | 16 08                                | 82 5                                  |                     | Edema of lung<br>Pleural effusion<br>Treated in oxygen chamber,<br>died |
|             |                     |                         | 30 5             |                |       |                               | 355 10          | 83 0 75                 | 1 31                           | 1 75                          | 10 86                           | 16 74                                | 64 9                                  |                     |   |
| 36217       | January 6           | 10                      | 35 0             | 104 0          | 120   | R U I<br>R M L<br>R I L       | 440 15          | 42 0 68                 | 1 02                           | 1 50                          | 14 35                           | 17 79                                | 80 7                                  |                     | Respirations very labored   |
|             |                     |                         | 31 5             |                |       |                               | 422 14          | 57 0 75                 | 1 03                           | 1 37                          |                                 |                                      |                                       |                     | Died  |
| 16259       | January 11          | 12                      | 25 0<br>22 0     | 101 4<br>101 4 | 128   | R L I                         | 375 9           | 38 0 91                 | 1 31                           | 1 44                          | 17 06                           | 19 24                                | 88 7                                  |                     | Pain Serum treatment<br>Recovered                                       |
|             |                     |                         |                  |                |       |                               | 357 7           | 86 0 99                 | 1 82                           | 1 84                          | 17 40                           | 20 00                                | 87 0                                  |                     |   |
| 56262       | January 17          | 10                      | 21 0<br>19 6     | 100 0          | 80    | R L L                         | 405 8           | 50 1 41                 | 1 71                           | 1 21                          | 16 69                           | 18 41                                | 90 7                                  |                     | Not acutely ill<br>Recovered  |
|             |                     |                         |                  |                |       |                               | 348 6           | 83 1 50                 | 2 12                           | 1 41                          | 17 06                           | 18 42                                | 92 6                                  |                     |   |
| 66264       | January 16          | 12                      | 40 0             | 103 0          | 108   | R U L<br>R L L                |                 |                         |                                |                               | 17 09                           | 20 08                                | 85 2                                  |                     | Died  |
|             |                     |                         | 42 0             | 103 8          | 120   |                               |                 |                         |                                |                               | 16 86                           | 20 05                                | 84 1                                  |                     |   |



TABLE I—Continued

| Case number | History | Date     | Dose of morphine | Respiratory rate | Temperature | Pulse | Area of pulmonary involvement | Tidal air | Minute volume | Duration of inspiration | Duration of expiration | Ratio inspiration to expiration | Oxygen content             | Oxygen capacity            | Per cent saturation | Remarks                     |
|-------------|---------|----------|------------------|------------------|-------------|-------|-------------------------------|-----------|---------------|-------------------------|------------------------|---------------------------------|----------------------------|----------------------------|---------------------|-----------------------------|
|             |         |          | mgm              |                  | °F          |       |                               | cc        | liters        | sec<br>onds             | sec<br>onds            |                                 | vol<br>umes<br>per<br>cent | vol<br>umes<br>per<br>cent |                     |                             |
| 156317      |         | March 13 | 16†              | 12 5             | 103 5       | 100   | L U L<br>L L L                | 278       | 11 83         | 0 66                    | 0 69                   | 1 05                            | 15 34                      | 17 23                      | 89 0                | Severe pain                 |
|             |         |          |                  | 31 1             |             |       |                               | 284       | 9 70          | 0 81                    | 0 92                   | 1 13                            | 15 10                      | 16 68                      | 90 6                | Recovered                   |
| 166352      |         | March 11 | 12               | 72 0             | 102 8       | 128   | L U L<br>I L L                | 127       | 9 14          | 0 52                    | 0 58                   | 1 11                            | 15 30                      | 19 26                      | 79 4                | Pain                        |
|             |         |          |                  | 64 0             |             |       | R M L                         | 174       | 11 03         | 0 44                    | 0 44                   | 1 00                            | 15 05                      | 19 94                      | 75 5                | Recovered                   |
| 176358      |         | March 20 | 16               | 44 0             | 104 6       | 96    | R U L                         |           |               |                         |                        |                                 | 13 75                      | 17 87                      | 76 9                | Rales throughout both lungs |
|             |         | March 20 |                  | 36 0             | 104 1       | 106   |                               |           |               |                         |                        |                                 | 13 96                      | 18 91                      | 73 5                | Recovered                   |
| 186439      |         | May 29   | 18               | 32 2             | 100 1       | 108   | L U L<br>L L L                | 331       | 10 67         | 0 85                    | 1 04                   | 1 22                            | 13 05                      | 14 18                      | 92 1                | Moist râles throughout      |
|             |         |          |                  | 25 1             |             |       | R U L<br>R M L                | 262       | 6 38          | 0 87                    | 1 77                   | 2 04                            | 11 47                      | 14 20                      | 80 8                | In sanitarium               |
| 196464      |         | June 9   | 18               | 24 2             | 99 8        | 82    | L L L                         | 304       | 7 37          | 1 10                    | 1 30                   | 1 18                            | 16 46                      | 19 05                      | 86 4                | Bronchopneumonia            |
|             |         |          |                  | 22 1             |             |       |                               | 236       | 5 21          | 1 04                    | 1 62                   | 1 56                            | 16 17                      | 18 90                      | 85 5                | Recovered                   |

\* The first observation of each pair was made before morphine was given, the second 15 to 30 minutes after

† 240 mgm caffeine

‡ Plus 192 mgm caffeine.

TABLE 1—Continued

| Case number | Date                 | Dose of morphine | Respiratory rate | Temperature    | Pulse     | Area of pulmonary involvement    | Tidal air     | Minute volume | Duration of inspiration | Duration of expiration | Ratio inspiration to expiration | Oxygen content               | Oxygen capacity              | Per cent saturation | Remarks                                  |
|-------------|----------------------|------------------|------------------|----------------|-----------|----------------------------------|---------------|---------------|-------------------------|------------------------|---------------------------------|------------------------------|------------------------------|---------------------|--|
|             |                      | mgm              |                  | °F             |           |                                  | cc            | liters        | sec<br>seconds          | sec<br>seconds         |                                 | vol.<br>times<br>per<br>cent | vol.<br>times<br>per<br>cent |                     |  |
| 156347      | March 13             | 16†              | 42 5<br>31 1     | 103 5          | 100       | L U L<br>L L L                   | 278 11<br>284 | 83 0<br>9 70  | 0 66<br>0 81            | 0 69<br>0 92           | 1 05<br>1 13                    | 15 34<br>15 10               | 17 23<br>16 68               | 89 0<br>90 6        | Severe pain<br>Recovered                 |
| 166352      | March 14             | 12               | 72 0<br>64 0     | 102 8          | 128       | L U L<br>I L L<br>R M L          | 127<br>174    | 9 14<br>11 03 | 0 52<br>0 44            | 0 58<br>0 44           | 1 11<br>1 00                    | 15 30<br>15 05               | 19 26<br>19 94               | 79 4<br>75 5        | Pain<br>Recovered                        |
| 176358      | March 20<br>March 20 | 16               | 44 0<br>36 0     | 104 6<br>104 1 | 96<br>106 | R U L                            |               |               |                         |                        |                                 | 13 75<br>13 96               | 17 87<br>18 91               | 76 9<br>73 5        | Rales throughout both lungs<br>Recovered |
| 186439      | May 29               | 18               | 32 2             | 100 1          | 108       | L U L<br>L L L<br>R U L<br>R M L | 331 10<br>262 | 67 0<br>6 38  | 85 1<br>0 87            | 0 4<br>1 77            | 1 22<br>2 04                    | 13 05<br>11 47               | 14 18<br>14 20               | 92 1<br>80 8        | Moist rales throughout<br>In sanitarium  |
| 196464      | June 9               | 18               | 24 2<br>22 1     | 99 8           | 82        | L L L                            | 304<br>236    | 7 37<br>5 21  | 1 10<br>1 04            | 1 30<br>1 62           | 1 18<br>1 56                    | 16 46<br>16 17               | 19 05<br>18 90               | 86 4<br>85 5        | Bronchopneumonia<br>Recovered            |

\* The first observation of each pair was made before morphine was given, the second 15 to 30 minutes after

† 240 mgm caffeine

‡ Plus 192 mgm caffeine.

morphine on the respiratory movements, and (II) the effect of morphine on the oxygen saturation of the arterial blood. The relationship of these two has been considered elsewhere (9). The data are tabulated in table 1.

1. *The respiratory movements* of 15 patients were studied in the plethysmograph before and after morphine administration.

*Rate.* In all but one case there was a drop in rate. The average drop in 14 cases was 4.1 to the minute. The greatest fall was from 12.5 to 3.1. In one patient (number 6289) the rate increased from 10 to 12 per minute. His tidal air, however, fell from 244 to 186 cc., and his minute volume from 9.78 to 7.81 liter. His breathing indicated edema of the lung, and at the time of observation he was rapidly growing worse. His arterial saturation dropped from 85.9 to 81.7 per cent after morphine, a change of little, if any, significance.

*Tidal air.* In 10 cases there was a drop in tidal air, the greatest drop being 138 cc. This occurred in patient number 6246, whose arterial saturation diminished 21.5 per cent. The average drop in tidal air was 57.7 cc. In the remaining 5 cases the tidal air increased, the greatest increase being 102 cc. In these 5 cases, pleuritic pain was a prominent symptom, and relief of pain by morphine probably allowed deeper breathing with more comfort. In one of the 5 cases 192 mgm. of caffeine were given with the morphine. These will be considered later. In no one of these 5 cases was the increase in arterial saturation as great as 4 per cent.

*Minute volume.* In 13 cases the minute volume was diminished after morphine. The greatest drop in minute volume was 4.95 liters and the smallest was 0.85 liter, the average being 2.20 liters.

Two patients (numbers 6295 and 6352) showed an increase in minute volume. In both of these the breathing was extremely shallow and the rate correspondingly rapid. In the one case the rate was 42.3 and the tidal air was 196 cc., while in the other the rate was 72 and the tidal air was 127 cc. In the first patient the minute volume increased from 8.22 to 10.51 liters, and in the second it increased from 9.14 to 11.03 liters. Both patients were very ill. The first had two lobes involved, and the second had three. In neither were there any signs of edema of the lungs. In the second patient there seems to have been a psychic element in the excessively rapid respirations,

morphine on the respiratory movements, and (II) the effect of morphine on the oxygen saturation of the arterial blood. The relationship of these two has been considered elsewhere (9). The data are tabulated in table 1.

1. The respiratory movements of 15 patients were studied in the plethysmograph before and after morphine administration.

*1. Rate.* In all but one case there was a drop in rate. The average drop in 14 cases was 4.1 to the minute. The greatest fall was from 12.5 to 3.1. In one patient (number 6289) the rate increased from 10 to 12 per minute. His tidal air, however, fell from 244 to 186 cc., and his minute volume from 9.78 to 7.81 liter. His breathing indicated edema of the lung, and at the time of observation he was rapidly growing worse. His arterial saturation dropped from 85.9 to 84.7 per cent after morphine, a change of little if any, significance.

*2. Tidal air.* In 10 cases there was a drop in tidal air, the greatest drop being 138 cc. This occurred in patient number 6246, whose arterial saturation diminished 21.5 per cent. The average drop in tidal air was 57.7 cc. In the remaining 5 cases the tidal air increased, the greatest increase being 102 cc. In these 5 cases, pleuritic pain was a prominent symptom, and relief of pain by morphine probably allowed deeper breathing with more comfort. In one of the 5 cases 192 mgm. of caffeine were given with the morphine. These will be considered later. In no one of these 5 cases was the increase in arterial saturation as great as 1 per cent.

*3. Minute volume.* In 13 cases the minute volume was diminished after morphine. The greatest drop in minute volume was 4.95 liters and the smallest was 0.85 liter, the average being 2.20 liters.

Two patients (numbers 6295 and 6352) showed an increase in minute volume. In both of these the breathing was extremely shallow and the rate correspondingly rapid. In the one case the rate was 42.3 and the tidal air was 196 cc., while in the other the rate was 72 and the tidal air was 127 cc. In the first patient the minute volume increased from 8.22 to 10.51 liters, and in the second it increased from 9.14 to 11.03 liters. Both patients were very ill. The first had two lobes involved, and the second had three. In neither were there any signs of edema of the lungs. In the second patient there seems to have been a psychic element in the excessively rapid respirations,

TABLE 2  
Data showing the average effect of several doses of morphine on the respirations of patients suffering from pneumonia

| History number | Total dose of morphine | Number of doses given | Area of pulmonary involvement | Average rate before morphine | Average rate $\frac{1}{2}$ to 14 hours after morphine | Change in rate | Rate before last dose | Rate after last dose | Change in rate | Number of hours during which morphine was given | Remarks  |
|----------------|------------------------|-----------------------|-------------------------------|------------------------------|---|----------------|-----------------------|----------------------|----------------|---|--|
| Group A        |                        |                       |                               |                              |   |                |                       |                      |                |   |  |
| 6259           | 28 mgm                 | 2                     | R L L                         | 28 5                         | 27 0  | -1 5           | 25 0                  | 22 0                 | -3 0           | 8   | Dry rales  |
| 6272           | 28                     | 3                     | L L L<br>L U L                | 42 7                         | 40 7  | -2 0           | 38 0                  | 38 0                 | 0              | 17  | Dry rales, friction rub  |
| 6316           | 56                     | 5                     | R, L L                        | 25 5                         | 24 0  | -1 5           | 24 0                  | 24 0                 | 0              | 120   | Dry rales, friction rub  |
| 6317           | 38                     | 3                     | L L L                         | 30 5                         | 29 0  | -1 5           | 34 0                  | 30 0                 | -4 0           | 30  | Dry rales  |
| 6335           | 40                     | 3                     | R, U L                        | 28 7                         | 26 6  | -2 1           | 24 0                  | 22 8                 | -1 2           | 22  | Dry rales  |
| 6347           | 36                     | 4                     | L U L<br>L L L                | 36 2                         | 30 5  | -5 7           | 36 0                  | 32 0                 | -4 0           | 70  | Dry rales  |
| 6352           | 22                     | 2                     | L U L<br>L L L<br>R, M L      | 59 0                         | 55 0  | -4 0           | 46 0                  | 46 0                 | 0              | 11  | Dry rales, friction rub  |
| 6368           | 30                     | 3                     | R, M L<br>R, L L              | 38 0                         | 36 0  | -2 0           | 40 0                  | 38 0                 | -2 0           | 43  | Dry rales, few moist rales at bases, pleural effusion, mitral stenosis |

TABLE 2  
Data showing the average effect of several doses of morphine on the respirations of patients suffering from pneumonia

| History number | Total dose of morphine | Number of doses given | Area of pulmonary involvement | Average rate before morphine | Average rate $\frac{1}{2}$ to 1 $\frac{1}{2}$ hours after morphine | Change in rate | Rate before last dose | Rate after last dose | Change in rate | Number of hours during which morphine was given | Remarks  |
|----------------|------------------------|-----------------------|-------------------------------|------------------------------|--|----------------|-----------------------|----------------------|----------------|---|--|
| Group A        |                        |                       |                               |                              |  |                |                       |                      |                |   |  |
| 6259           | 28<br>mgm              | 2                     | R L L                         | 28 5                         | 27 0   | -1 5           | 25 0                  | 22 0                 | -3 0           | 8   | Dry râles  |
| 6272           | 28                     | 3                     | L L L<br>L U L                | 42 7                         | 40 7   | -2 0           | 38 0                  | 38 0                 | 0              | 17  | Dry râles, friction rub  |
| 6316           | 56                     | 5                     | R L L                         | 25 5                         | 24 0   | -1 5           | 24 0                  | 24 0                 | 0              | 120   | Dry râles, friction rub  |
| 6317           | 38                     | 3                     | L L L                         | 30 5                         | 29 0   | -1 5           | 34 0                  | 30 0                 | -4 0           | 30  | Dry râles  |
| 6335           | 40                     | 3                     | R U L                         | 28 7                         | 26 6   | -2 1           | 24 0                  | 22 8                 | -1 2           | 22  | Dry râles  |
| 6347           | 36                     | 4                     | L U L<br>L L L                | 36 2                         | 30 5   | -5 7           | 36 0                  | 32 0                 | -4 0           | 70  | Dry râles  |
| 6352           | 22                     | 2                     | L U L<br>L L L<br>R M L       | 59 0                         | 55 0   | -4 0           | 46 0                  | 46 0                 | 0              | 11  | Dry râles, friction rub  |
| 6368           | 30                     | 3                     | R M L<br>R L L                | 38 0                         | 36 0   | -2 0           | 40 0                  | 38 0                 | -2 0           | 43  | Dry râles, few moist râles at bases, pleural effusion, mitral stenosis |

TABLE 2—Continued

| History number    | Total dose of morphine | Number of doses given | Area of pulmonary involvement               | Average rate before morphine | Average rate $\frac{1}{2}$ to 1 $\frac{1}{2}$ hours after morphine | Change in rate | Rate before last dose | Rate after last dose | Change in rate | Number of hours during which morphine was given | Remarks  |
|-------------------|------------------------|-----------------------|---|------------------------------|--|----------------|-----------------------|----------------------|----------------|---|--|
| Group B—Continued |                        |                       |   |                              |  |                |                       |                      |                |   |  |
| 6439              | 54                     | 4                     | R U L<br>R. M L<br>R. L L<br>L U L<br>L L L | 41.5                         | 35.8   | -5.7           | 32.2                  | 25.1                 | -7.1           | 432   | Extensive involvement, many moist râles, tuberculosis                                    |
| 6451              | 62                     | 6                     | R U L<br>R M L<br>R L L                     | 38.0                         | 30.8   | -7.2           | 40.0                  | 38.0                 | -2.0           | 158   | Moist râles. Treated in oxygen chamber   |
| Group C           |                        |                       |   |                              |  |                |                       |                      |                |   |  |
| 6264              | 78                     | 7                     | R. U L<br>R L L                             | 44.4                         | 45.2   | +0.8           | 42.0                  | 48.0                 | +6.0           | 108   | Moist and musical râles throughout both lungs, very jaundiced. Treated in oxygen chamber |
| 6289              | 36                     | 3                     | R U L<br>R L L                              | 45.3                         | 43.3   | -2.0           | 48.0                  | 48.0                 | 0              | 10  | Moist râles throughout. Treated in oxygen chamber  |
| 6291              | 94                     | 10                    | R. U L<br>R. L L                            | 39.4                         | 37.4   | -2.0           | 60.0                  | 48.0                 | -12.0          | 192   | Fraction rub, pleural effusion, moist râles. Treated in oxygen chamber                   |

TABLE 2—Continued

| History number    | Total dose of morphine | Number of doses given | Area of pulmonary involvement               | Average rate before morphine | Average rate $\frac{1}{2}$ to 14 hours after morphine | Change in rate | Rate before last dose | Rate after last dose | Change in rate | Number of hours during which morphine was given  | Remarks |
|-------------------|------------------------|-----------------------|---|------------------------------|---|----------------|-----------------------|----------------------|----------------|--|---------|
| Group B—Continued |                        |                       |   |                              |   |                |                       |                      |                |  |         |
| 6439              | 54                     | 4                     | R U L<br>R. M L<br>R. L L<br>L U L<br>L L L | 41 5                         | 35 8  | -5 7 32        | 2 25 1                | -7 1                 | 432            | Extensive involvement, many moist râles, tuberculosis                                    |         |
| 6451              | 62                     | 6                     | R U L<br>R M L<br>R L L                     | 38 0                         | 30 8  | -7 2 40        | 0 38 0                | -2 0                 | 158            | Moist râles. Treated in oxygen chamber   |         |
| Group C           |                        |                       |   |                              |   |                |                       |                      |                |  |         |
| 6264              | 78                     | 7                     | R. U L<br>R L L                             | 44 4                         | 45 2  | +0 8 42        | 0 48 0                | +6 0                 | 108            | Moist and musical râles throughout both lungs, very jaundiced. Treated in oxygen chamber |         |
| 6289              | 36                     | 3                     | R U L<br>R L L                              | 45 3                         | 43 3  | -2 0 48        | 0 48 0                | 0                    | 10             | Moist râles throughout. Treated in oxygen chamber  |         |
| 6291              | 94                     | 10                    | R. U L<br>R. L L                            | 39 4                         | 37 4  | -2 0 60        | 0 48 0                | -12 0                | 192            | Friction rub, pleural effusion, moist râles. Treated in oxygen chamber                   |         |



cluded in the table We believe that this delayed slowing of the rate is in part at least due to the cumulative action of morphine

We have also studied the effect of caffeine on the respiratory movements and arterial saturation of one patient (number 7347) He was observed on 2 successive days while acutely ill On the first day he was given 240 mgm of caffeine sodium benzoate, and on the second day he was given 192 mgm of caffeine and 12 mgm of morphine After caffeine alone, his rate, tidal air, minute volume, and per cent saturation increased, while the morphine and caffeine together resulted in a reduction in rate, but a slight increase in tidal air and per cent saturation The minute volume on this occasion was smaller after the drug was given than before None of these changes was of sufficient magnitude to attach much importance to them, but at least they are different from those observed after morphine alone That codeine in moderate amounts may have a detrimental effect on the respiratory center is suggested by case number 6213, whose respiratory rate dropped to 14 and whose arterial saturation dropped to 40 per cent after he had had 24 mgm of morphine in addition to 236 mgm of codeine, which he had received during a period of  $3\frac{1}{2}$  days His breathing was of the Cheyne-Stokes type, his lungs were filling with exudate, he rapidly passed into coma, and, had he not been immediately put into the oxygen chamber, he would in all probability have died The next morning, while breathing a 40 per cent oxygen mixture, his arterial saturation was 90.3 per cent and his respiratory rate was 18

*II Effect of morphine on the oxygen saturation of the arterial blood*  
In 16 patients out of 20 on whom oxygen analyses of the arterial blood were done before and after morphine, there was a drop in the arterial saturation The greatest drop was 21.3 per cent and the average drop was 5 per cent (table 1) Of the remaining 4 cases, 3 showed a slight rise in  $O_2$  saturation after morphine In one no analysis was made One of these 3 cases (number 6232) had severe pain, which was relieved by morphine His tidal air increased from 412 to 438 cc, though his minute volume dropped from 13.35 to 10.96 liters Another, case number 6262, was not acutely ill, and the third (case number 6347) was given caffeine with the morphine Moreover, in his case pain was relieved by morphine and his tidal air increased

cluded in the table We believe that this delayed slowing of the rate is in part at least due to the cumulative action of morphine

We have also studied the effect of caffeine on the respiratory movements and arterial saturation of one patient (number 7347) He was observed on 2 successive days while acutely ill On the first day he was given 240 mgm of caffeine sodium benzoate, and on the second day he was given 192 mgm of caffeine and 12 mgm of morphine After caffeine alone, his rate, tidal air, minute volume, and per cent saturation increased, while the morphine and caffeine together resulted in a reduction in rate, but a slight increase in tidal air and per cent saturation The minute volume on this occasion was smaller after the drug was given than before None of these changes was of sufficient magnitude to attach much importance to them, but at least they are different from those observed after morphine alone That codeine in moderate amounts may have a detrimental effect on the respiratory center is suggested by case number 6213, whose respiratory rate dropped to 14 and whose arterial saturation dropped to 40 per cent after he had had 24 mgm of morphine in addition to 236 mgm of codeine, which he had received during a period of  $3\frac{1}{2}$  days His breathing was of the Cheyne-Stokes type, his lungs were filling with exudate, he rapidly passed into coma, and, had he not been immediately put into the oxygen chamber, he would in all probability have died The next morning, while breathing a 40 per cent oxygen mixture, his arterial saturation was 90.3 per cent and his respiratory rate was 18

*II Effect of morphine on the oxygen saturation of the arterial blood*  
In 16 patients out of 20 on whom oxygen analyses of the arterial blood were done before and after morphine, there was a drop in the arterial saturation The greatest drop was 21.3 per cent and the average drop was 5 per cent (table 1) Of the remaining 4 cases, 3 showed a slight rise in  $O_2$  saturation after morphine In one no analysis was made One of these 3 cases (number 6232) had severe pain, which was relieved by morphine His tidal air increased from 412 to 438 cc, though his minute volume dropped from 13.35 to 10.96 liters Another, case number 6262, was not acutely ill, and the third (case number 6347) was given caffeine with the morphine Moreover, in his case pain was relieved by morphine and his tidal air increased

lungs breath sounds were bronchovesicular and numerous rhonchi were heard. She appeared cyanotic. Blood culture was positive for Type II pneumococcus. She was transferred to the oxygen chamber on the day the morphine test was made. The next day her arterial saturation was 93.2 per cent. Five days later she died. (3) In patient number 6439 the saturation fell from 92.1 to 80.8 per cent. He had been acutely ill for 12 days. Tubercle bacilli had been demonstrated in his sputum. His temperature fluctuated from 101° to 104°F. The only uninvolved part of his lungs was the lower right lobe, which was clear when the arterial punctures were done. Moist râles were present throughout both lungs. Figure 1, *a* and *b*, shows parts of his respiratory tracing before and after morphine administration. These 3 patients in whom morphine administration resulted in a definite and perhaps serious unsaturation of the arterial blood were all extremely ill. Moreover, they showed not only extensive lung involvement, but the presence of diffuse, moist râles. It is to be noted that in none was anoxemia severe before morphine. A fourth case already referred to is not included here, since no arterial blood analysis was made before morphine. After morphine injection, however, his saturation was only 40 per cent.

#### DISCUSSION

In most cases of pneumonia the effect of morphine on the respiratory movements and on the arterial oxygen saturation is slight. Certainly the depression of respiration which follows morphine administration is ordinarily not sufficient to contraindicate its use. The benefits which may accrue to the patient in the direction of relief from pain, reduction of metabolism, and sleep, undoubtedly outweigh the possible ill effects of a slight reduction in pulmonary ventilation and increase of anoxemia.

Occasionally, however, morphine may so diminish pulmonary ventilation as to result in serious oxygen want. This is liable to occur in patients in whom the pulmonary involvement is extensive and is accompanied by diffuse moisture, and in patients who are already suffering from severe oxygen want. Because of the possibility of this type of reaction to it, morphine must always be used with caution and is best combined with oxygen therapy.

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In spite of the wide use of oxygen in pneumonia, comparatively few figures have been published concerning the degree of arterial oxygen unsaturation which occurs in the disease or the changes in saturation which follow oxygen therapy. Our study presents the results of over 300 arterial punctures and oxygen analyses made in 137 patients. The paper is divided into two parts, the first dealing with frequency tables having to do with the distribution of arterial oxygen saturations and a consideration of them in relation to the type of invading organism, survival of patients, and the effect of oxygen inhalation. The second part of the paper deals with a description of a few individual cases selected because of their extreme anoxemia and because in several of them autopsies were performed and long findings observed not long after the oxygen analyses of the arterial blood were performed.

#### MATERIAL AND METHODS

The patients studied were all admitted to the Hospital of The Rockefeller Institute with the diagnosis of acute pneumonia. The great majority were pneumonias of the lobar type, though in a few the distribution of the signs and the clinical history were that of bronchopneumonia. No selection was made in this series with the exception that in general arterial bleedings were performed on the more seriously ill and on those with the more intense cyanosis.

The blood was usually obtained from the femoral artery with the technique suggested by Fraser (9). No harm or inconvenience was ever found to come from this procedure in approximately 300 punctures. One patient was bled nine times in 12 days without ill effect. The blood was transferred from the syringe to small tonometers, where it was oxalated and kept over mercury. In most instances duplicate analyses of oxygen content and capacity were

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Stadie (8) observed in a series of 33 pneumonia cases that there was only one case which recovered in which the arterial unsaturation of the blood was greater than 20 per cent. It would be of interest to know whether in a larger series the degree of anoxemia and mortality showed as close a correlation even though they may not be caus-

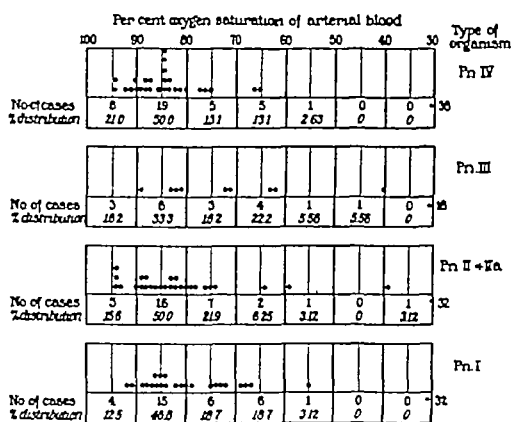


FIG 2 FREQUENCY TABLE SHOWING DISTRIBUTION OF PER CENT OXYGEN SATURATION OF ARTERIAL BLOOD ARRANGED ACCORDING TO THE TYPE OF INFECTING ORGANISM

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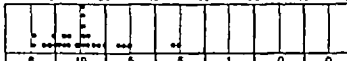
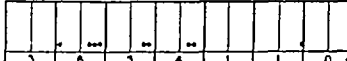
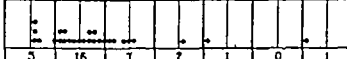

| Per cent oxygen saturation of arterial blood                                      |      |      |      |      |      |      |   |      |    | Type of organism |
|---|------|------|------|------|------|------|---|------|----|------------------|
| 100 90 80 70 60 50 40 30  |      |      |      |      |      |      |   |      |    |                  |
|  |      |      |      |      |      |      |   |      |    | Pn IV            |
| No. of cases  | 6    | 19   | 5    | 5    | 1    | 0    | 0 | 0    | 30 |                  |
| % distribution  | 21.0 | 59.0 | 15.1 | 15.1 | 2.63 | 0    | 0 | 0    |    |                  |
|  |      |      |      |      |      |      |   |      |    | Pn III           |
| No. of cases  | 3    | 6    | 3    | 4    | 1    | 1    | 0 | 0    | 18 |                  |
| % distribution  | 16.2 | 33.3 | 16.2 | 22.2 | 5.56 | 5.56 | 0 | 0    |    |                  |
|  |      |      |      |      |      |      |   |      |    | Pn II + IIa      |
| No. of cases  | 5    | 16   | 7    | 2    | 1    | 0    | 0 | 1    | 32 |                  |
| % distribution  | 15.6 | 50.0 | 21.9 | 6.25 | 3.12 | 0    | 0 | 3.12 |    |                  |
|  |      |      |      |      |      |      |   |      |    | Pn I             |
| No. of cases  | 4    | 15   | 6    | 6    | 1    | 0    | 0 | 0    | 32 |                  |
| % distribution  | 12.5 | 46.9 | 18.7 | 18.7 | 3.12 | 0    | 0 | 0    |    |                  |

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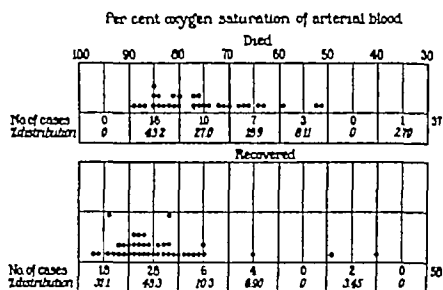


FIG 4 FREQUENCY TABLE SHOWING COMPARISON OF DISTRIBUTION OF ARTERIAL OXYGEN SATURATION IN FATAL AND RECOVERED CASES NOT TREATED BY TYPE I ANTIPNEUMOCOCCUS SERUM

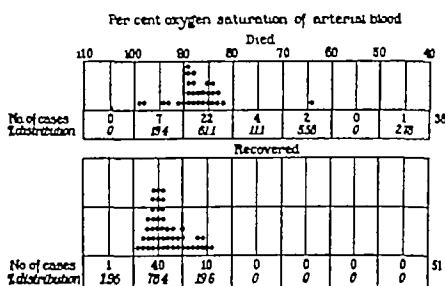


FIG 5 FREQUENCY TABLE SHOWING DISTRIBUTION OF ARTERIAL OXYGEN SATURATION IN PATIENTS AFTER EXPOSURE TO 40± PER CENT OXYGEN COMPARISON OF FATAL AND RECOVERED CASES

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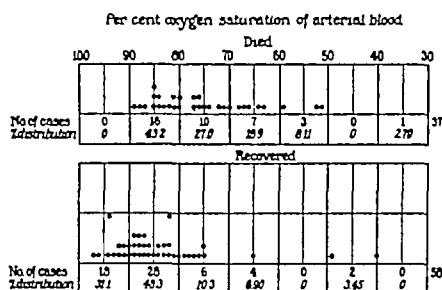


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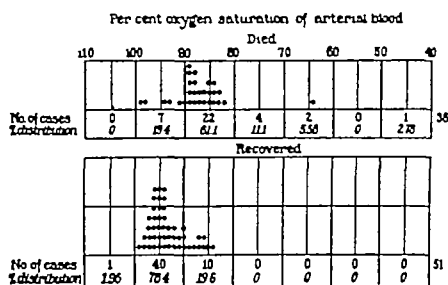


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## PART II

Eight of 130 cases tabulated in figure 1 showed an oxygen saturation below 60 per cent. A more detailed consideration of these cases will be profitable both from the point of view of inquiring into the causes of anoxemia and of explaining why certain patients, when placed in the chamber, exhibit no increase in the per cent oxygen saturation of their arterial blood.

*Case 1 (Hospital No 5811) Lobar pneumonia, septicemia (Pneumococcus Type II) Died*

The patient was a male, aged 37, who entered the hospital after 2 days of acute illness. On admission there was slight cyanosis and evidence of pneumonic consolidation of the upper two-thirds of the right lung. Three days later the patient's condition became definitely worse. Cyanosis was intense and diffuse and the patient could be aroused only with difficulty. The signs in the right chest had extended to the base, where many medium and coarse râles could be heard.

The arterial blood was only 39.4 per cent saturated with oxygen, the content and capacity being 5.94 and 15.06 vols per cent respectively. At this time the patient was breathing 30 to the minute. He was transferred to the oxygen chamber and kept in an atmosphere containing 42 per cent oxygen until he died, approximately 16 hours later. One and one-half hours after admission to the chamber the arterial  $O_2$  content was 14 vols per cent, the capacity 16.7 vols per cent and the per cent saturation 83.8. The respiratory rate at this time was 36. Twelve hours before death blood culture showed 29 colonies of Type II pneumococcus per cubic centimeter of blood. No permission for autopsy was granted.

*Comment*

The significant feature of this case is the intense anoxemia coming on simultaneously with a spread to the right lower lobe. The fact that in this region there was only moderate dulness but many medium and coarse râles appears to be of importance. It is this type of freshly spread early lesion in the presence of a heavy blood invasion which is so frequently associated with intense arterial anoxemia.

*Case 2 (Hospital No 5418) Lobar pneumonia (Pneumococcus Type II) Died*

The patient, a male, aged 56, entered the hospital on the second day of illness. There was evidence of pneumonic consolidation in the right lower lobe, with coarse râles and a friction rub to be heard in the left scapular region. The patient's condition gradually became worse. Four days later both lungs were full

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*Case 4 (Hospital No 5413) Male, aged 52 Lobar pneumonia (Pneumococcus Type III) Died*

The patient came to the hospital on the third day of illness. There was marked diffuse cyanosis. The arterial blood was 52.1 per cent saturated. Signs of consolidation were confined to the lower right back, where there were numerous moist râles. Musical râles were scattered throughout the chest on both sides and expiration was prolonged.

The patient was transferred to the oxygen chamber, which was charged to 41.5 per cent O<sub>2</sub>. Twelve hours later dyspnea and cyanosis were unimproved. Breathing was asthmatic. Breath sounds were suppressed over the lower half of the right chest in back, where there were dulness and fine râles. There was much mucus in the upper respiratory tract. The O<sub>2</sub> content was now 12.45 and capacity 13.75 vols per cent. The per cent saturation was therefore 90.6. The next 12 hours brought a distinct change for the worse. The patient's face was purple and he was gasping for breath. Loud tracheal râles were present. Examination of the chest was not satisfactory because of patient's condition. Blood culture showed 10 colonies of *Pneumococcus* Type III per cubic centimeter of blood. The arterial blood had dropped to a saturation of 62.5 per cent, the content and capacity being 4.40 and 7.05 respectively.

At autopsy the left lung was found to be quite normal and weighed 550 grams. The right lung, however, weighed over 2 kilograms. On section all three lobes appeared to be equally consolidated. The cut surface was firm, granular, dark reddish and quite moist. Frothy, bloody fluid exuded from the smaller bronchi.

### *Comment*

The first response to oxygen was a satisfactory one as far as the saturation of the arterial blood was concerned. With increasing amount of moisture in the air spaces of the right lung aeration of the blood was impeded and marked anoxemia occurred in spite of oxygen inhalation. The autopsy findings provided a satisfactory explanation for this, there being an involvement of the entire right lung which contained no air and much fluid.

*Case 5 (Hospital No 5490) Female, aged 48 Lobar pneumonia (Pneumococcus Type I) Recovered*

Four days before admission the patient had a sudden shaking chill. On admission she appeared to be very ill. There was intense cyanosis of the finger tips. Signs of consolidation were present in the left lower lobe. Blood culture showed 3 colonies of *Pneumococcus* Type I per cubic centimeter. The following day the patient's condition was somewhat worse. Blood culture was still positive. She was very cyanotic. Temperature was 103.4°F, pulse 130, respirations 38. The arterial saturation was 55.2 per cent, O<sub>2</sub> content 6.76 and O<sub>2</sub> capacity 12.26 vols.

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to be only 48.9 per cent saturate.  $O_2$  content was 6.43 vols per cent, capacity 13.15. The patient was transferred to the oxygen chamber and exposed to 41.5 per cent  $O_2$ . The next morning, 12½ hours later, his temperature had dropped to 98.8°F, pulse 88 and respirations 24. The oxygen saturation was now 86.1 per cent,  $O_2$  content 9.62 and capacity 11.15 vols per cent. Only a trace of cyanosis remained. Two days later the patient was removed from the chamber. He soon became slightly cyanosed about the face and nail beds and did not look nearly so well as when in the chamber. However, he made a steady recovery.

### Comment

This case is typical of the influenzal bronchopneumonias in which extreme oxygen want is a prominent feature with pulmonary signs characterized by widespread coarse râles rather than evidence of localized consolidation. It is these patients for whom oxygen therapy is especially useful. The drop in temperature following admission to the chamber is, in the light of Boothby's observations (5), perhaps more than a coincidence.

*Case 7 (Hospital No 6213) Male, aged 49. Lobar pneumonia (Pneumococcus Type III). Recovered.*

The patient was taken sick 3 days before he entered the hospital. On admission on December 1, 1927, he showed only slight cyanosis of the lips and nail beds. At this time the lung signs consisted of suppression of breath sounds and friction rub in the right axilla, with dulness and almost completely suppressed breath sounds in the right back, below the angle of the scapula. Two days later cyanosis was slightly increased and the physical signs suggested a spread to the upper lobe of the right lung. Numerous dry râles were now present. X-ray showed opacity throughout the right upper lobe and parts of middle and lower lobes. The next day the patient was obviously worse. There had been a still further spread in the right axilla. Cough was very troublesome, and it was necessary to give codeine. At 9.15 p.m. he was given 12 mgm of morphine. Not long after the patient's respiratory rate dropped to 10, cyanosis became intense, and he developed Cheyne-Stokes breathing. His lungs were filling with fluid and he rapidly passed into coma. An arterial puncture showed the blood to be only 40.2 per cent saturated with oxygen, the content being 6.86 vols per cent and the capacity 17.08.

He was hurriedly transferred to the oxygen chamber with immediately beneficial results. The cyanosis almost completely disappeared, respirations became regular and increased in rate to 28 and there was a striking improvement in the patient's psyche. Arterial blood drawn 12 hours after admission to the chamber showed an increase in saturation of 125 per cent. The oxygen content was now 10.59 vols per cent, the capacity 11.74 vols per cent and the per cent saturation 90.3. This was true in spite of the fact that the physical signs showed a still fur-

to be only 48.9 per cent saturate.  $O_2$  content was 6.43 vols per cent, capacity 13.15. The patient was transferred to the oxygen chamber and exposed to 41.5 per cent  $O_2$ . The next morning, 12½ hours later, his temperature had dropped to 98.8°F, pulse 88 and respirations 24. The oxygen saturation was now 86.1 per cent,  $O_2$  content 9.62 and capacity 11.15 vols per cent. Only a trace of cyanosis remained. Two days later the patient was removed from the chamber. He soon became slightly cyanosed about the face and nail beds and did not look nearly so well as when in the chamber. However, he made a steady recovery.

### Comment

This case is typical of the influenzal bronchopneumonias in which extreme oxygen want is a prominent feature with pulmonary signs characterized by widespread coarse râles rather than evidence of localized consolidation. It is these patients for whom oxygen therapy is especially useful. The drop in temperature following admission to the chamber is, in the light of Boothby's observations (5), perhaps more than a coincidence.

*Case 7 (Hospital No 6213) Male, aged 49 Lobar pneumonia (Pneumococcus Type III) Recovered*

The patient was taken sick 3 days before he entered the hospital. On admission on December 1, 1927, he showed only slight cyanosis of the lips and nail beds. At this time the lung signs consisted of suppression of breath sounds and friction rub in the right axilla, with dulness and almost completely suppressed breath sounds in the right back, below the angle of the scapula. Two days later cyanosis was slightly increased and the physical signs suggested a spread to the upper lobe of the right lung. Numerous dry râles were now present. X-ray showed opacity throughout the right upper lobe and parts of middle and lower lobes. The next day the patient was obviously worse. There had been a still further spread in the right axilla. Cough was very troublesome, and it was necessary to give codeine. At 9.15 p.m. he was given 12 mgm of morphine. Not long after the patient's respiratory rate dropped to 10, cyanosis became intense, and he developed Cheyne-Stokes breathing. His lungs were filling with fluid and he rapidly passed into coma. An arterial puncture showed the blood to be only 40.2 per cent saturated with oxygen, the content being 6.86 vols per cent and the capacity 17.08.

He was hurriedly transferred to the oxygen chamber with immediately beneficial results. The cyanosis almost completely disappeared, respirations became regular and increased in rate to 28 and there was a striking improvement in the patient's psyche. Arterial blood drawn 12 hours after admission to the chamber showed an increase in saturation of 125 per cent. The oxygen content was now 10.59 vols per cent, the capacity 11.74 vols per cent and the per cent saturation 90.3. This was true in spite of the fact that the physical signs showed a still fur-

## DISCUSSION

A statistical estimate of the therapeutic value of oxygen in pneumonia would at present have little value. The number of cases is far too small for such an analysis and the character of the material too complex. We have had to content ourselves with the construction of simple frequency tables to study the per cent distribution of the various grades of anoxemia. There appears to be a positive correlation between anoxemia and mortality. Moreover, the level of oxygen saturation in the arterial blood of a patient exposed to 40 per cent oxygen is of prognostic importance, since the survivors usually reach a level above 90 per cent, while the fatal cases do so far less often.

We have made no effort to give complete clinical reports on all our cases because the space available will not permit this. Furthermore, an analysis of this sort is extremely confusing. The patient's condition alters so quickly in pneumonia that one can seldom be sure whether the changes observed after exposure to oxygen are determined by this or are part of the normal variations of the disease. In general we may state that, aside from conspicuous improvement in color, the other changes usually encountered were slight diminution in pulse and respiratory rate and improvement in the patient's mental state. These observations are in agreement with those observed by the authors already referred to. Boothby's recent finding (5) of a reduction of fever following oxygen administration is of much interest. That this has not been striking on our cases may perhaps be accounted for by the fact that they were mostly lobar pneumonias seen as a rule on the third to fifth day of disease and not post-operative bronchopneumonias placed in a chamber shortly after the diagnosis was made.

In a small group of cases selected because of severe anoxemia (oxygen saturation below 60 per cent) we have considered the physical signs and autopsy findings in relation to the arterial oxygen saturation. The presence of extensive, rapidly spreading pulmonary lesions with much moisture, exudate or transudate, appears to be common to this group. In what manner this type of lesion brings about anoxemia we are not yet certain. It is in part due to diminished lung volume, in part due to passage of blood through unaerated channels. Such a

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Inability to correlate satisfactorily the experimental observations of Birkhaug with the well established clinical phenomena of erysipelas has led to the present study. Three aspects of the subject have been investigated: (1) the reactivity of the skin of erysipelas patients to intracutaneous injections of filtrates of erysipelas streptococci, (2) the presence of a toxic substance in the blood of patients acutely ill with erysipelas, and (3) the capacity of the serum of erysipelas patients to neutralize the toxic action of culture filtrates.

#### SKIN REACTIVITY OF PATIENTS WITH ERYSIPELAS TO FILTRATES OF ERYSIPELAS STREPTOCOCCI

The skin reactions to sterile filtrates from broth cultures of erysipelas streptococci were studied in 30 patients with erysipelas at intervals during the acute and convalescent stages of the disease. With the exception the patients were all on the adult medical wards of the New Haven Hospital, their ages ranging from 13 to 70 years. The filtrates employed in most instances were prepared in our laboratory from cultures of hemolytic streptococci cultivated directly from the lesions of typical cases of erysipelas. For comparison a standardized erysipelas toxin obtained from the Squibb Laboratories through the courtesy of Dr. J. F. Anderson was used in some of the cases.

*Preparation and standardization of filtrates.* Flasks containing 2 cc. of 1 per cent defibrinated rabbit's blood, buffered, meat infusion broth, pH 7.4 to 7.6, were inoculated with 2.5 cc. of an 18 hour broth culture of erysipelas streptococci. After incubation for 48 hours at 37°C. the culture was passed through a Berkefeld filter, the filtrate tested for sterility and bottled. The filtrates were standardized in terms of skin test doses per cubic centimeter by injecting 0.1 cc. of graded dilutions in the skin of the most reactive individual available. One-tenth cubic centimeter of that dilution which caused a local erythema approximately 10 mm. in diameter 24 hours after injection

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The results as charted demonstrate that 20 cases (Group I) showed on the first test during the active stage of the disease either no reaction or only a very slight degree of reactivity of somewhat doubtful

|          |          | DAY OF DISEASE |    |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|----------|----------|----------------|----|----|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|----|--|--|-------|----|--|
|          | CASE NO. | 1              | 2  | 3  | 4 | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 30+ |    |  |  |       |    |  |
|          |          |                |    |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
| GROUP I  | 1        |                |    | -  |   |    | ±  |    |    |    | ±± |    |    |    | ±± |    |    |    | ±± |    |    |    | +  |    |    |    |    |    |    |    | ±± |     |    |  |  |       |    |  |
|          | 2        |                |    | -  |   |    |    |    |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 3        |                | -  |    |   |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 4        |                | -  |    |   |    | ±± |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 5        |                | ±± |    |   | ±± |    |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 6        |                |    | -  |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 7        |                |    | +  |   |    |    |    |    | ±± |    |    |    | +  |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 8        |                |    | ±± |   |    |    | ±± |    | ±± |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 9        |                |    | -  |   |    |    |    | -  |    |    |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 10       |                |    | -  |   |    |    | +  |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 11       |                |    | -  |   |    |    |    |    |    |    |    | -  |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 12       | -              |    |    |   | -  |    |    |    | -  |    |    | -  |    |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 13       | -              |    |    |   |    |    |    |    |    | ±± |    | -  |    |    |    | ±± |    |    |    | +  |    |    | +  |    |    |    |    |    |    | -  |     | ±± |  |  |       |    |  |
|          | 14       |                |    |    |   | ±± |    |    |    |    | ±± |    |    |    |    | ±± | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 15       | -              |    |    | - |    |    |    |    | -  |    |    |    |    | +  |    |    | ±± |    |    |    | ±± |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 16       |                |    | ±± |   |    |    |    |    |    |    |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       | ±± |  |
|          | 17       |                |    |    |   | ±± |    |    |    |    | ±± |    |    |    | ±± |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       | ±± |  |
|          | 18       |                |    | ±± |   |    |    |    |    |    |    |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 19       |                | ±± |    |   | ±± |    |    |    | -  |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  | 40 42 |    |  |
|          | 20       |                |    |    |   |    | -  |    |    | -  |    |    |    |    |    |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       | -  |  |
|          | 21       | ±±             | ±± |    |   |    |    | ±± |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 22       | ±±             | ±± |    |   |    |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 23       |                |    | +  |   |    |    |    | ±± |    | ±± |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 24       |                |    | +  |   |    |    |    | ±± |    | ±± |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 25       | ±±             |    |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
| GROUP II | 26       |                |    | ±± |   |    |    |    | ±± |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 27       |                |    |    |   |    |    |    | ±± |    | ±± |    |    |    |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 28       |                |    | ±± |   |    |    |    | ±± |    | ±± |    |    |    |    |    |    | ±± |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 29       |                |    | ±± |   |    |    |    |    |    |    |    | -  |    |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 30       |                |    | ±± |   |    | ±± |    |    |    |    |    |    | -  |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
|          | 30+      |                |    |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
| TOTAL    |          | 26             |    |    |   |    |    |    |    |    |    | 27 |    |    |    |    |    |    |    |    |    | 28 |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
| ±±±      |          | 7              |    |    |   |    |    |    |    |    |    | 9  |    |    |    |    |    |    |    |    |    | 13 |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
| +        |          | 2              |    |    |   |    |    |    |    |    |    | 7  |    |    |    |    |    |    |    |    |    | 8  |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |
| ±±       |          | 17             |    |    |   |    |    |    |    |    |    | 11 |    |    |    |    |    |    |    |    |    | 7  |    |    |    |    |    |    |    |    |    |     |    |  |  |       |    |  |

CHART 1 SKIN REACTIVITY OF ERYSIPELAS PATIENTS

- = non-reactive, ± = reactive to 30 or 50 S T D , + = reactive to 10 S T D , ±± = reactive to 3 or 5 S T D , ++ = reactive to 1 S T D The broken staggered lines mark the end of 7 and 15 day periods, respectively, after return of temperature to normal

significance, since the 30 to 50 S T D required the use of a 1 10 dilution of the filtrate They furthermore show that 10 cases (Group II) possessed some degree of reactivity Of the patients in this group 2





relationship between the stage of the disease and the degree of susceptibility to the filtrate exhibited by the study as a whole

|           |    | DAY OF DISEASE |   |    |    |    |   |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|-----------|----|----------------|---|----|----|----|---|----|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|------|-----|--|
| CASE NO.  |    | 1              | 2 | 3  | 4  | 5  | 6 | 7  | 8 | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30   | 30+ |  |
| GROUP I   | 21 | ++             |   |    | ++ |    |   | ++ |   |    | ++ |    |    |    | ++ |    |    | ++ |    |    | +  |    |    |    |    |    |    |    |    | ++ |      |     |  |
|           | 1  |                | - |    |    |    |   | ++ |   |    | ++ |    |    |    | ++ |    |    |    | ++ |    |    | +  |    |    |    |    |    |    |    | ++ |      |     |  |
|           | 22 | ++             |   |    |    |    |   |    |   |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 4  |                | - |    |    | ++ |   |    |   |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 5  | ±              |   |    |    | ++ |   |    |   |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 7  |                | - |    | +  |    |   |    |   | ++ |    |    |    | +  |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 23 |                |   | +  |    |    |   | *  |   |    |    |    | -  | *  |    | *  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 24 |                |   | +  |    |    |   | *  |   |    |    |    |    |    |    | *  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 25 | ++             |   |    |    |    |   | ++ |   |    | ++ |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 26 |                |   | ++ |    | -  |   | ++ |   |    |    |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 10 |                | - |    |    |    | + |    |   |    |    |    | *  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 11 |                |   | -  |    |    |   | +  |   |    |    |    |    | -  |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 27 |                |   |    |    |    |   | ++ |   |    | ++ |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 28 |                |   | ++ |    |    |   | ++ |   |    | ++ |    |    |    |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    | ++ |      |     |  |
| GROUP II  | 2  |                | - |    |    |    |   | -  |   |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 6  |                |   | -  |    |    |   | -  |   |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 8  |                | ± |    |    |    |   | ±  |   |    |    | *  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 12 | -              |   |    | -  |    |   |    | - |    |    |    | -  |    |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 13 | -              |   |    |    | -  |   |    |   |    |    |    | -  |    |    |    |    | -  |    |    | +  |    | +  |    |    |    |    |    | -  | ++ |      |     |  |
|           | 14 |                |   |    |    | ±  |   |    |   |    | ++ |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 15 | -              |   |    | -  |    |   |    | - |    |    |    |    |    | +  |    | *  |    | *  |    | *  |    |    |    |    |    |    |    |    |    |      |     |  |
| GROUP III | 16 |                | ± |    |    |    |   |    |   |    |    |    |    | ±  |    |    |    | *  |    |    |    | *  |    |    |    |    | ++ |    |    |    | ++   |     |  |
|           | 18 |                |   | ±  |    |    |   |    |   |    |    |    |    | ±  |    |    |    |    |    |    |    |    |    |    |    |    |    | ++ |    |    |      |     |  |
|           | 29 |                |   | ±  |    |    |   |    |   |    |    |    | -  |    | ±  |    |    |    |    |    |    |    |    |    |    |    |    | ++ |    |    |      |     |  |
|           | 30 |                | ± |    |    | ±  |   |    |   |    |    | -  |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |     |  |
|           | 19 |                | ± |    |    | ±  |   |    |   |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 4042 |     |  |
|           | 20 |                |   |    |    |    | - |    |   |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | -  |    |    |      | -   |  |

CHART 2 RELATIONSHIP OF SKIN REACTIVITY TO CLINICAL COURSE OF ERYSIPELAS

Case 1 Readmission of Case 13 Recurrence on 8th day of 24 hour's duration Case 13 Recurrences on the 20th and 29th days both of which lasted approximately 48 hours Case 29 Abscess developed about left eye on 8th day and was incised on the 12th day Case 30 On the 16th day patient had recurrence over entire area previously involved and at that time a blood culture yielded hemolytic streptococci The recurrence lasted 36 hours Case 19 Abscesses developed on arms beginning on the 7th day Hemolytic streptococcus septicaemia developed on the 13th day Exitus on the 18th day Case 20 Migrating erysipelas with metritis, arthritis and septicemia complicating pregnancy and the puerperium Recovery on 42nd day

In chart 2 the cases have been rearranged into three groups in order to bring out more clearly the relationship between the skin tests and the course of the disease In Group I are the 14 cases which showed

relationship between the stage of the disease and the degree of susceptibility to the filtrate exhibited by the study as a whole

|           |    | DAY OF DISEASE |    |    |   |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|-----------|----|----------------|----|----|---|----|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|------|--|--|
| CASE NO.  |    | 1              | 2  | 3  | 4 | 5  | 6 | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 30+  |  |  |
| GROUP I   | 21 | ++             |    | ++ |   |    |   | ++ |    |    | ++ |    |    |    | ++ |    |    |    | ++ |    |    | +  |    |    |    |    |    |    |    |    | ++ |      |  |  |
|           | 1  |                | -  |    |   | ++ |   |    |    | ++ |    |    |    | ++ |    |    |    |    | ++ |    |    |    | +  |    |    |    |    |    |    |    | ++ |      |  |  |
|           | 22 | ++             |    |    |   |    |   |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 4  |                | -  |    |   | ++ |   |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 5  | ±              |    |    |   | ++ |   |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 7  |                | -  |    | + |    |   |    | ++ |    |    |    | +  |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 23 |                |    | +  |   |    |   | +  |    |    |    | -  | +  |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 24 |                |    | +  |   |    |   | +  |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 25 | ++             |    |    |   |    |   | ++ |    | ++ |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 26 |                |    | ++ |   | -  |   | ++ |    | ++ |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 10 |                |    | -  |   |    |   | +  |    | +  |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 11 |                |    | -  |   |    |   | +  |    | +  |    |    | -  |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 27 |                |    |    |   |    |   | ++ |    | ++ |    | ++ |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 28 |                | ++ |    |   |    |   | ++ |    | ++ |    |    |    |    | ++ |    |    |    |    | ++ |    |    |    |    |    |    |    |    |    | ++ |    |      |  |  |
| GROUP II  | 2  |                | -  |    |   |    |   | -  |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 6  |                |    | -  |   |    |   | -  |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 8  |                | +  |    |   |    |   | +  |    | +  |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 12 | -              |    |    | - |    |   |    | -  |    |    | +  |    |    |    |    | +  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 13 | -              |    |    |   | -  |   |    |    |    |    |    | -  |    |    |    |    |    |    |    |    | +  |    | +  |    |    |    |    |    |    |    | ++   |  |  |
|           | 14 |                |    |    |   | ±  |   |    |    |    | ±  |    |    |    | ++ |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 15 | -              |    |    | - |    |   |    |    | -  |    |    |    | +  |    |    | +  |    |    |    |    | +  |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 16 |                | ±  |    |   |    |   |    |    |    |    |    |    |    | ±  |    |    |    |    |    |    |    |    |    |    |    | ++ |    |    |    |    | ++   |  |  |
| GROUP III | 18 |                | ±  | ++ |   |    |   |    |    |    |    |    |    |    | ±  |    |    |    |    |    |    |    |    |    |    |    |    | ++ |    |    |    |      |  |  |
|           | 29 |                | ++ |    |   |    |   |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 30 |                | ++ |    |   | ±  |   |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |
|           | 19 |                | ±  |    |   | ±  |   |    |    |    |    | -  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 4042 |  |  |
|           | 20 |                |    |    |   |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | -    |  |  |
|           |    |                |    |    |   |    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |      |  |  |

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In chart 2 the cases have been rearranged into three groups in order to bring out more clearly the relationship between the skin tests and the course of the disease In Group I are the 14 cases which showed

patient 10 STD of erysipelas streptococcus culture filtrate in a volume of 0.5 cc was added, so that 0.1 cc of the mixture contained 1 STD of the filtrate and 0.05 cc of serum. With the last of the series of sera from each patient an additional mixture of a comparable amount of the serum and of a heated filtrate was made. The mixtures

|          |         | DAY OF DISEASE   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|----------|---------|--|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|--|---|----|----|--|--|
|          | CASE NO | 1  | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 30+ |  |   |    |    |  |  |
|          |         |  |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
| GROUP I  | 21      |  | N | P |   |   |   |   |   | O |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 22      |  | N | O |   |   |   | N |   | O |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 2       |  | N |   |   | O |   |   | I |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 3       |  | P |   |   |   |   |   | P |   |    | I  |    |    |    |    | I  |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 4       |  |   |   | N |   |   |   | N |   |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 6       |  |   | P | N |   |   |   | N |   |    |    |    | P  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 7       |  |   | N | P |   |   |   |   | I |    |    |    |    | I  |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 23      |  |   | N |   |   |   |   |   |   |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 8       |  | P | P |   |   |   | P |   |   |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 31      |  | N | N |   |   |   | O |   |   |    |    |    | I  |    |    |    | I  |    |    |    | I  |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 12      |  | N |   |   | N |   |   | P |   |    |    |    | O  |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 27      |  |   |   |   |   | N |   | N |   | N  |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 29      |  |   |   | N |   |   |   |   |   |    |    |    | N  |    |    |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 14      |  |   |   | N |   |   |   |   |   |    |    |    |    | O  |    |    | O  |    |    |    |    | O  |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 32      |  | N |   |   |   |   | P | O |   |    |    |    |    | N  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 16      |  |   | P | N |   | O |   |   |   |    | O  |    |    |    |    |    |    |    |    |    |    | O  |    |    |    | O  |    |    |    |    |     |  |   | O  | 37 |  |  |
|          | 33      |  |   |   | N |   |   |   |   |   |    | I  |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 18      |  |   | P |   |   |   | P |   |   |    |    |    |    |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    | I  |    | I   |  |   |    |    |  |  |
|          | 20      |  |   |   |   |   |   | N |   |   |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | O  |    | O   |  | O | 55 |    |  |  |
| 5        |         | O  |   |   |   | O |   |   |   |   | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
| 24       |         |  |   | O |   |   | O |   |   |   |    | I  |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
| GROUP II | 25      |  | O |   |   |   |   |   | N |   |    |    |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 10      |  |   | O |   |   |   | O |   |   |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 26      |  |   |   | O |   |   |   | I |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 17      |  |   |   | O |   | O |   | O |   | P  |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 34      |  |   |   |   |   |   |   |   | O |    |    |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          | 19      |  |   | O |   | P |   |   |   |   |    | O  |    |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |
|          |         | <div>N - COMPLETE NEUTRALIZATION<br/>P - PARTIAL NEUTRALIZATION<br/>O - NO NEUTRALIZATION<br/>I - REACTION GREATER THAN TOXIN CONTRL</div> |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |  |   |    |    |  |  |

CHART 3 NEUTRALIZING CAPACITY OF THE SERUM OF ERYSIPELAS PATIENTS

Case numbers up to 27 agree with those of charts 1 and 2

were thoroughly shaken and heated at 37°C for one hour. One-tenth cubic centimeter of each mixture was injected into the skin of individuals reactive to 1 STD of filtrate. In addition 1 STD of the filtrate alone was injected at the same time for comparison.

patient 10 STD of erysipelas streptococcus culture filtrate in a volume of 0.5 cc was added, so that 0.1 cc of the mixture contained 1 STD of the filtrate and 0.05 cc of serum. With the last of the series of sera from each patient an additional mixture of a comparable amount of the serum and of a heated filtrate was made. The mixtures

|          |    | DAY OF DISEASE  |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|----------|----|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|---|--|--|-----------------|--|--|
| CASE NO  |    | 1   | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 30+ |   |  |  |                 |  |  |
| GROUP I  | 21 |   | N |   | P |   |   |   |   |   | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 22 |   | N | O |   |   |   |   | N |   |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 2  |   | N |   |   | O |   |   |   |   | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 3  |   | P |   |   |   |   |   |   | P |    |    | I  |    |    |    |    | I  |    |    |    |    |    | O  |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 4  |   |   | N |   |   |   |   |   | N |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 6  |   |   | P | N |   |   |   |   | N |    |    |    | P  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 7  |   |   | N |   | P |   |   |   |   | I  |    |    |    | I  |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 23 |   |   | N |   |   |   |   |   |   |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 8  |   | P |   | P |   |   |   | P |   |    |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 31 |   | N |   | N |   |   |   | O |   |    |    |    | I  |    |    |    |    | I  |    |    |    |    | I  |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 12 | N   |   |   |   | N |   |   |   | P |    |    |    | O  |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 27 |   |   |   |   |   |   | N |   | N |    | N  |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 29 |   |   |   | N |   |   |   |   |   |    |    | N  |    |    |    |    |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 14 |   |   |   | N |   |   |   |   |   |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 32 | N   |   |   |   |   |   | P |   | O |    |    |    |    | N  |    |    |    |    |    |    |    | N  |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 16 |   |   | P |   | N |   | O |   |   |    |    | O  |    |    |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |     |   |  |  | O <sup>37</sup> |  |  |
|          | 33 |   |   |   | N |   |   |   |   |   |    |    | I  |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 18 |   |   |   | P |   |   |   | P |   |    |    |    |    |    |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    | I  |     | I |  |  |                 |  |  |
|          | 20 |   |   |   |   |   | N |   |   |   |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  | O <sup>58</sup> |  |  |
| GROUP II | 5  |   | O |   |   |   | O |   |   |   | O  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 24 |   |   |   | O |   |   |   | O |   |    |    | I  |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 25 |   |   | O |   |   |   |   |   | N |    |    |    |    |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 10 |   |   | O |   |   |   |   | O |   |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 26 |   |   |   | O |   |   |   |   | I |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 17 |   |   |   | O |   | O |   | O |   |    | P  |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          | 34 |   |   |   |   |   |   |   |   |   | O  |    |    |    |    |    |    |    |    |    |    |    |    | O  |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
| 19       |    |   | O |   |   | P |   |   |   |   |    | O  |    |    |    |    |    |    | I  |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |
|          |    | <div>N - COMPLETE NEUTRALIZATION<br/>P - PARTIAL NEUTRALIZATION<br/>O - NO NEUTRALIZATION<br/>I - REACTION GREATER THAN TOXIN CONTROL</div> |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |   |  |  |                 |  |  |

CHART 3 NEUTRALIZING CAPACITY OF THE SERUM OF ERYSIPELAS PATIENTS  
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## DISCUSSION

The three important phenomena brought to light in the preceding observations, namely, the tendency for the cutaneous reactivity of erysipelas patients to become more marked during convalescence the absence of a demonstrable toxin in the circulating blood of patients in the acute stage of the disease, and the neutralization of erysipelas streptococcus culture filtrates by the serum of most patients in the acute phase of the disease with apparent loss of this power during convalescence, fail to support Birkhaug's concept of erysipelas as a specific toxemia, recovery from which is due to the development of an antitoxic immunity

The results of the skin tests suggest, rather, that an increasing sensitiveness or allergy to streptococcus products, presumably liberated at the site of the erysipelatous lesion, develops with the progress of the disease to convalescence and recovery. The fairly definite correlation between the rapidity with which skin reactivity developed and the clinical course of the disease, as shown in chart 2, furthermore suggests that the development of tissue allergy may play at least a part, perhaps an important part, in the mechanism of recovery from the infection. That the skin reactions were neutralizable not only in sensitive normal individuals but also in sensitive patients in the convalescent period, as proved to be the case on a number of tests, is not surprising, since it has been shown by Dochez and Stevens (10) that the skin reactions of rabbits rendered allergic to undiluted culture filtrates of erysipelas streptococci, are neutralizable during the early phase of sensitivity.

The negative results of the tests for toxin in the circulating blood early in the disease indicate that a specific toxemia in the sense in which it has been shown to occur in scarlet fever (9), plays little or no significant part in erysipelas. This view is further supported by the neutralization tests, in which it is shown that the majority of adult patients with erysipelas already possess early in the disease sufficient circulating antibody to neutralize 20 S.T.D. of filtrate per cubic centimeter of blood. The toxigenic activity of erysipelas streptococci, in most instances relatively poorly developed as compared with that of most scarlatinal streptococci, is probably counteracted at the

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out above, that they do not strictly parallel each other and that no simple relationship exists. It is suggested that a satisfactory correlation may be established by recognition of the probability that three immunity states—antitoxic immunity, tissue allergy, and humoral allergy—are concerned and that the time of appearance of each in measureable amount is variable and independent of the others. Such variation in the rate and development of immunity states and their mutual independence is well recognized. Besredka and Nakagawa (11) have stated that the cutaneous mechanism of defense is not, in general, associated with circulating antibodies. Swift, Derick and Hitchcock (12) have found that focal infections induce and maintain cutaneous reactivity, which may be diminished or destroyed by intra-

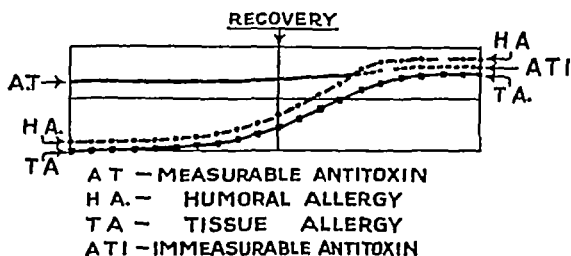


FIG 1 DEVELOPMENT OF IMMUNITY STATES IN ERYSIPELAS

At the point at which the line HA crosses the line AT the neutralization of toxin is obscured and the antitoxin becomes immeasurable

venous injections of the organisms concerned. Gay and Rhodes (13) have reported that subcutaneous immunization may protect the skin against a lethal dose of the homologous organism, but not protect against an intravenous injection of a similar dose, and, conversely, that intravenous immunization may not protect against a lethal dose given subcutaneously.

If, then, it be assumed that the rate of development and degree of tissue allergy as measured by the skin tests, of antitoxic immunity as measured by the neutralization tests, and of humoral allergy as measured by the apparent loss of the neutralizing capacity of the serum, are variable and mutually independent, any variation in the results can be explained. To do so in each case would be impossible within the limits of this report. The most frequent relationship and

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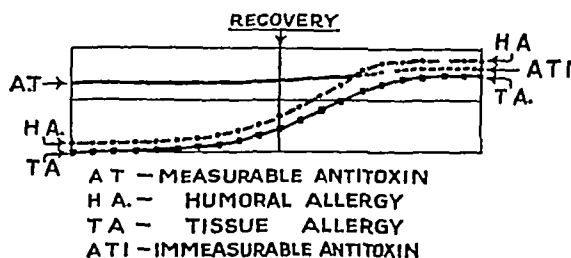


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The relations between systemic blood pressure and the cardiac output per minute and per beat is of interest and the administration of atropine affords an opportunity to study these relations also. The effect of atropine on systemic blood pressure has been studied by Harris (5) in normal adults and by Sturgis, Wearn and Tompkins (6) in patients with "effort syndrome". Harris observed that the subcutaneous injection of 1.2 mgm of atropine was followed by a fall in systolic pressure and a decrease in the pulse pressure. He inferred that the output of the heart was diminished. A similar decrease after a similar dose was found by Sturgis, Wearn and Tompkins (6) in patients with effort syndrome.

Many studies have been made of the effect of atropine on the heart rate. It is important to note that doses of different magnitude may have opposite effects on the heart rate. As pointed out by McGuigan (7) small doses (0.4 to 0.6 mgm) may decrease the rate or leave it unchanged while a dose of 1.2 mgm usually suffices to increase it considerably.

#### METHODS

Observations on the cardiac output, heart rate, metabolic rate, and systemic blood pressure were made before and after the intravenous injection of 1.2 mgm of atropine sulphate. In a preliminary experiment 2.4 mgm were injected but this amount rendered the subject so restless and uncomfortable that the observations were not comparable with those made before the injection when the subject was quiet and at ease.

The output of the heart was measured by the method of Field, Bock, Gildea and Lathrop (8). All observations were made in the morning with the subject having had no food for at least 12 hours and after he had rested 30 to 45 minutes in the reclining position, in which he remained while the observations were made. Each subject was trained in the necessary respiratory manoeuvres before the cardiac output was actually measured. Then a preliminary measurement was made and if the subject showed himself well trained the complete experiment was carried out on the following day. The order of procedure was as follows: first the samples of alveolar and "mixed venous" gases were collected, then the expired air was collected for a six minute period, and finally the blood pressure was taken. At short intervals during these observations the pulse was counted. These counts were averaged and the result is designated the "average pulse rate".

When this control observation was completed 1.2 mgm of atropine sulphate were given intravenously and the observations immediately repeated, with the addition of several measurements of the blood pressure during the procedure.

A third series of observations was made 1 to 1½ hours after injection of atropine.

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TABLE 1

*The effect of injecting atropine upon the pulse rate, respiratory quotient, metabolic rate, excretion of CO<sub>2</sub>, arterio-venous difference, and cardiac output per minute and per beat*

|                       | Average pulse rate | Respiratory quotient | Basal metabolic rate | CO <sub>2</sub> excreted per minute | A V difference   | Cardiac output per minute | Cardiac output per beat |
|-----------------------|--------------------|----------------------|----------------------|-------------------------------------|------------------|---------------------------|-------------------------|
|                       |                    |                      | per cent             | cc                                  | volumes per cent | cc                        | cc                      |
| Subject 1 (W G)       |                    |                      |                      |                                     |                  |                           |                         |
| March 17, 8 30 a m    | 72                 | 0 81                 | -14                  | 181                                 | 3 11             | 5,820                     | 81                      |
| March 18, 9 30 a m.   | 67                 | 0 80                 | -15                  | 178                                 | 3 15             | 5,650                     | 84                      |
| March 18, 10 10 a m * | 110                | 0 80                 | -12                  | 185                                 | 2 60             | 7,110                     | 65                      |
| March 18, 11 20 a m.  | 85                 | 0 83                 | -17                  | 177                                 | 2 52             | 7,020                     | 83                      |
| Subject 2 (F N)       |                    |                      |                      |                                     |                  |                           |                         |
| March 24, 8 30 a m.   | 76                 | 0 76                 | +2                   | 193                                 | 3 61             | 5,350                     | 70                      |
| March 25, 8 45 a m.   | 79                 | 0 79                 | +0                   | 191                                 | 3 96             | 4,820                     | 61                      |
| March 25, 9 42 a m.*  | 112                | 0 72                 | -2                   | 179                                 | 2 84             | 6,300                     | 56                      |
| March 25, 11 00 a m   | 84                 | 0 76                 | -8                   | 174                                 | 2 88             | 6,040                     | 72                      |
| Subject 3 (T A)       |                    |                      |                      |                                     |                  |                           |                         |
| March 31, 8 30 a m.   | 65                 | 0 81                 | -15                  | 182                                 | 4 62             | 3,940                     | 60                      |
| April 1, 10 40 a m *  | 93                 | 0 78                 | -11                  | 186                                 | 3 65             | 5,100                     | 55                      |
| April 1, 11 48 a m.   | 75                 | 0 79                 | -14                  | 179                                 | 3 32             | 5,390                     | 72                      |
| April 10, 8 30 a m.   | 62                 | 0 89                 | -15                  | 189                                 | 4 37             | 4,320                     | 70                      |
| Subject 4 (M H)       |                    |                      |                      |                                     |                  |                           |                         |
| April 14, 8 30 a m.   | 64                 | 0 83                 | -13                  | 198                                 | 5 01             | 3,950                     | 62                      |
| April 15, 8 15 a m.   | 61                 | 0 84                 | -12                  | 203                                 | 5 02             | 4,040                     | 66                      |
| April 15, 9 15 a m *  | 91                 | 0 84                 | -12                  | 199                                 | 4 62             | 4,300                     | 47                      |
| April 15, 10 36 a m.  | 74                 | 0 82                 | -14                  | 191                                 | 3 72             | 5,140                     | 69                      |
| Subject 5 (C K)       |                    |                      |                      |                                     |                  |                           |                         |
| April 22, 8 30 a m.   | 71                 | 0 84                 | -19                  | 177                                 | 4 10             | 4,320                     | 61                      |
| April 23, 9 00 a m.   | 65                 | 0 86                 | -16                  | 185                                 | 4 74             | 3,900                     | 60                      |
| April 23, 10 19 a m.* | 115                | 0 86                 | -20                  | 176                                 | 5 15             | 3,420                     | 30                      |
| April 23, 11 50 a m.  | 81                 | 0 84                 | -25                  | 162                                 | 5 06             | 3,200                     | 40                      |
| Subject 6 (C B)       |                    |                      |                      |                                     |                  |                           |                         |
| May 6, 8 00 a m.      | 63                 | 0 87                 | -17                  | 173                                 | 3 73             | 4,650                     | 74                      |
| May 6, 9 00 a m.*     | 104                | 0 76                 | -14                  | 160                                 | 2 90             | 5,520                     | 53                      |
| May 6, 10 20 a m.     | 76                 | 0 74                 | -21                  | 144                                 | 3 27             | 4,400                     | 58                      |
| May 6, 11 50 a m.     | 66                 | 0 77                 | -15                  | 158                                 | 3 45             | 4,580                     | 69                      |

\* 1 to 2 minutes before this time the subject received an intravenous injection of 1 2 mgm. atropine sulphate Immediately thereafter the determination of the cardiac output was begun

TABLE 1

*The effect of injecting atropine upon the pulse rate, respiratory quotient, metabolic rate, excretion of CO<sub>2</sub>, arterio-venous difference, and cardiac output per minute and per beat*

|                       | Average pulse rate | Respiratory quotient | Basal metabolic rate | CO <sub>2</sub> excreted per minute | A V difference   | Cardiac output per minute | Cardiac output per beat |
|-----------------------|--------------------|----------------------|----------------------|-------------------------------------|------------------|---------------------------|-------------------------|
|                       |                    |                      | per cent             | cc                                  | volumes per cent | cc                        | cc                      |
| Subject 1 (W G)       |                    |                      |                      |                                     |                  |                           |                         |
| March 17, 8 30 a m    | 72                 | 0 81                 | -14                  | 181                                 | 3 11             | 5,820                     | 81                      |
| March 18, 9 30 a m.   | 67                 | 0 80                 | -15                  | 178                                 | 3 15             | 5,650                     | 84                      |
| March 18, 10 10 a m * | 110                | 0 80                 | -12                  | 185                                 | 2 60             | 7,110                     | 65                      |
| March 18, 11 20 a m.  | 85                 | 0 83                 | -17                  | 177                                 | 2 52             | 7,020                     | 83                      |
| Subject 2 (F N)       |                    |                      |                      |                                     |                  |                           |                         |
| March 24, 8 30 a m.   | 76                 | 0 76                 | +2                   | 193                                 | 3 61             | 5,350                     | 70                      |
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| Subject 3 (T A)       |                    |                      |                      |                                     |                  |                           |                         |
| March 31, 8 30 a m.   | 65                 | 0 81                 | -15                  | 182                                 | 4 62             | 3,940                     | 60                      |
| April 1, 10 40 a m *  | 93                 | 0 78                 | -11                  | 186                                 | 3 65             | 5,100                     | 55                      |
| April 1, 11 48 a m.   | 75                 | 0 79                 | -14                  | 179                                 | 3 32             | 5,390                     | 72                      |
| April 10, 8 30 a m.   | 62                 | 0 89                 | -15                  | 189                                 | 4 37             | 4,320                     | 70                      |
| Subject 4 (M H)       |                    |                      |                      |                                     |                  |                           |                         |
| April 14, 8 30 a m.   | 64                 | 0 83                 | -13                  | 198                                 | 5 01             | 3,950                     | 62                      |
| April 15, 8 15 a m.   | 61                 | 0 84                 | -12                  | 203                                 | 5 02             | 4,040                     | 66                      |
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| Subject 5 (C K)       |                    |                      |                      |                                     |                  |                           |                         |
| April 22, 8 30 a m.   | 71                 | 0 84                 | -19                  | 177                                 | 4 10             | 4,320                     | 61                      |
| April 23, 9 00 a m.   | 65                 | 0 86                 | -16                  | 185                                 | 4 74             | 3,900                     | 60                      |
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| April 23, 11 50 a m.  | 81                 | 0 84                 | -25                  | 162                                 | 5 06             | 3,200                     | 40                      |
| Subject 6 (C B)       |                    |                      |                      |                                     |                  |                           |                         |
| May 6, 8 00 a m.      | 63                 | 0 87                 | -17                  | 173                                 | 3 73             | 4,650                     | 74                      |
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\* 1 to 2 minutes before this time the subject received an intravenous injection of 1 2 mgm. atropine sulphate Immediately thereafter the determination of the cardiac output was begun

*The metabolic rate*

No constant change in the metabolic rate was observed following the administration of atropine. In fact, the average rates just before and just after injection were identical. As is usual with trained subjects the basal rates are uniformly low. The respiratory minute volume increased on the average 4 per cent, which fits in with the absence of change in metabolic rate.

*The blood pressure*

It is realized that figures for the diastolic pressure are not accurate because of the difficulty of recognizing the diastolic point by the usual criteria. This difficulty we attempted to minimize by having all

TABLE 2

*Percentage changes in pulse rate and cardiac output per minute and per beat following the injection of 1.2 mgm. atropine sulphate intravenously*

|                           | Subject |     |     |     |     |     | Average |
|---------------------------|---------|-----|-----|-----|-----|-----|---------|
|                           | 1       | 2   | 3   | 4   | 5   | 6   |         |
| Pulse rate per minute     | +57     | +45 | +46 | +45 | +69 | +65 | +56     |
| Cardiac output per minute | +24     | +24 | +23 | +8  | -17 | +19 | +14     |
| Cardiac output per beat   | -22     | -15 | -15 | -27 | -51 | -28 | -26     |

pressures taken with the same mercury manometer and by the same observer. Even so, successive observations sometimes showed a striking lack of agreement. Our observations on the effect of atropine on the blood pressure are summarized in tables 3 and 4.

Table 3 shows the blood pressure reading just before and for some twenty minutes after the administration of the drug, with simultaneous pulse rates. It emphasizes the striking lack of correlation between heart rate and blood pressure in that the former may nearly double without change in the latter. In two instances there was a definite rise in both systolic and diastolic pressures.

Table 4 represents averages of all the pulse pressure figures obtained before and after injecting atropine. No constant change was observed but the average pulse pressures before and after atropine are nearly identical. The systolic pressures before giving atropine vary from

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|---------------------------|---------|-----|-----|-----|-----|-----|---------|
|                           | 1       | 2   | 3   | 4   | 5   | 6   |         |
| Pulse rate per minute     | +57     | +45 | +46 | +45 | +69 | +65 | +56     |
| Cardiac output per minute | +24     | +24 | +23 | +8  | -17 | +19 | +14     |
| Cardiac output per beat   | -22     | -15 | -15 | -27 | -51 | -28 | -26     |

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Table 4 represents averages of all the pulse pressure figures obtained before and after injecting atropine. No constant change was observed but the average pulse pressures before and after atropine are nearly identical. The systolic pressures before giving atropine vary from



95 to 110 mm This range of pressure is that usually found in healthy young men under standard basal conditions

### DISCUSSION

The administration of atropine, according to these observations, increases the rate of the heart relatively much more than the output of the heart per minute and thus produces a diminution in the output of the heart per beat This fact emphasizes the importance of the filling of the heart in relation to its output, and thus the importance of the factors determining the venous pressure These factors include gravity, the aspirating action of the thorax and the contraction of the muscles of the body as well as the pumping force of ventricular systole Atropine has, of course, effects other than acceleration of the heart

TABLE 4

*The pulse pressure (in millimeters of mercury) before and after the intravenous injection of 12 mgm atropine sulphate Each figure represents the average of several measurements*

|                             | Subject |    |    |    |    |    | Average |
|-----------------------------|---------|----|----|----|----|----|---------|
|                             | 1       | 2  | 3  | 4  | 5  | 6  |         |
| Before atropine             | 31      | 38 | 28 | 38 | 35 | 37 | 34.5    |
| Immediately after atropine  | 25      | 44 | 40 | 34 | 30 | 33 | 34.3    |
| 1 to 2 hours after atropine | 30      | 45 | 27 | 28 | 32 | 30 | 32.0    |

These include according to Cushny (9) a sedative action on many organs containing unstriated muscle, a decrease of most secretions, and a stimulation of the central nervous system, particularly the motor divisions of the brain These effects, particularly the last, which is presumably responsible for the restlessness sometimes observed in our experiments, may possibly affect the filling of the heart and thus account for the small but definite increase which was observed

The oxygen consumption of the resting human heart, according to Bainbridge (10) is about 12.5 cc per minute This amount is approximately 5 per cent of the total oxygen consumption of the body per minute This being true small changes in the work of the heart can hardly be recognized by changes in the total oxygen consumption The unchanging metabolic rate in these experiments cannot be taken as evidence that the work of the heart was not increased

The absence of constant changes in the blood pressure levels indi-

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|-----------------------------|---------|----|----|----|----|----|---------|
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| Before atropine             | 31      | 38 | 28 | 38 | 35 | 37 | 34.5    |
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at 1½ hour intervals on January 31, 1927 in which the variation in the output of the heart was only 100 cc

This general agreement constitutes not only a demonstration of the degree of perfection of physiological regulation but also impres-

TABLE 1  
*The output of the heart per minute and related figures*

| Date              | Method               | Pulse rate | Basal metabolic rate      | Respiratory quotient | Oxygen per minute | Carbon dioxide per minute | Arterio-venous difference oxygen | Arterio-venous difference carbon dioxide | Output per beat | Output per minute |
|-------------------|----------------------|------------|---------------------------|----------------------|-------------------|---------------------------|----------------------------------|--|-----------------|-------------------|
|                   |                      |            | <i>per cent of normal</i> |                      | <i>cc</i>         | <i>cc</i>                 | <i>vol-umes per cent</i>         | <i>vol-umes per cent</i>                 | <i>cc</i>       | <i>cc</i>         |
| March 31, 1923    | Burwell and Robinson | 67         | -10                       | 0.78                 | 238               | 186                       | 6.44                             | 5.02*                                    | 59              | 3,700             |
| April 17, 1923    | Burwell and Robinson | 66         | -8                        | 0.85                 | 236               | 200                       | 5.91                             | 5.02*                                    | 60              | 3,940             |
| April 19, 1923    | Burwell and Robinson | 68         | -10                       | 0.81                 | 236               | 191                       | 5.97                             | 4.48*                                    | 58              | 3,950             |
| June 2, 1923      | Burwell and Robinson | 72         | -10                       | 0.78                 | 238               | 186                       | 6.01                             | 4.69*                                    | 55              | 3,960             |
| March 13, 1924    | Burwell and Robinson | 66         | -8                        | 0.78                 | 248               | 193                       | 6.33                             | 4.94*                                    | 57              | 3,920             |
| January 31, 1927  |                      |            |                           |                      |                   |                           |                                  |  |                 |                   |
| 8 30 a m          | Bock et al           | 68         | -5                        | 0.81                 | 243               | 197                       | 6.19*                            | 5.01                                     | 58              | 3,930             |
| 10 00 a m         | Bock et al           | 68         | -4                        | 0.80                 | 247               | 198                       | 6.46*                            | 5.17                                     | 56              | 3,830             |
| 11 30 a m         | Bock et al           | 68         | -4                        | 0.80                 | 249               | 199                       | 6.38*                            | 5.10                                     | 57              | 3,900             |
| March 21, 1927    | Bock et al           | 67         | -6                        | 0.79                 | 246               | 194                       | 6.30*                            | 4.97                                     | 58              | 3,900             |
| June 14, 1927     | Bock et al.          | 73         | -10                       | 0.81                 | 232               | 188                       | 4.43*                            | 3.59                                     | 72              | 5,240             |
| June 16, 1927     | Bock et al           | 67         | -10                       | 0.81                 | 236               | 191                       | 4.77*                            | 3.86                                     | 74              | 4,950             |
| June 24, 1927     | Bock et al           | 71         | -7                        | 0.82                 | 243               | 199                       | 5.16*                            | 4.23                                     | 66              | 4,700             |
| February 10, 1928 | Bock et al.          | 65         | -8                        | 0.83                 | 231               | 192                       | 6.38*                            | 5.29                                     | 56              | 3,630             |

\* Calculated

sive evidence of the agreement in this subject, of two quite different methods of measuring the output of the heart

Why three successive measurements during ten days in June 1927 should have given higher figures than any other of the thirteen is not known. The weather at this period was warm but the tempera-

at  $1\frac{1}{2}$  hour intervals on January 31, 1927 in which the variation in the output of the heart was only 100 cc

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| Date              | Method               | Pulse rate | Basal metabolic rate | Respiratory quotient | Oxygen per minute | Carbon dioxide per minute | Arterio-venous difference oxygen | Arterio-venous difference carbon dioxide | Output per beat | Output per minute |
|-------------------|----------------------|------------|----------------------|----------------------|-------------------|---------------------------|----------------------------------|--|-----------------|-------------------|
|                   |                      |            | per cent of normal   |                      | cc                | cc                        | vol-umes per cent                | vol-umes per cent                        | cc              | cc                |
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normal level In this respect, it is similar to a slow change in the myxedematous condition of the tissues

The change appears to persist as long as the metabolism is held at a normal level by the administration of thyroid extract

TABLE 1

| Case number | Name        | Age | Laboratory number | Before administration of thyroid extract |   | After administration of thyroid extract |   |
|-------------|-------------|-----|-------------------|--|---|---|---|
|             |             |     |                   | Basal metabolic rate                     | Concentration of protein* in spinal fluid | Basal metabolic rate                    | Concentration of protein* in spinal fluid |
|             |             |     |                   | <i>per cent of normal</i>                | <i>mgm per 100 cc</i>                     | <i>per cent of normal</i>               | <i>mgm per 100 cc</i>                     |
| 1           | Mr J G      | 53  | 4236              | -26                                      | 221                                       | -3                                      | 49  |
| 2           | Mrs J W     | 50  | 4224              | -21                                      | 129                                       | +2                                      | 58  |
| 3           | Mr H L      | 21  | 4302              | -34                                      | 111                                       | +19                                     | 30  |
| 4           | Mrs M V L   | 47  | 3984              | -17                                      | 93  | +23                                     | 32  |
| 5           | Mrs M B     | 30  | 4533              | -40                                      | 80  | -12                                     | 43  |
| 6           | Mrs L C     | 53  | 4532              | -46                                      | 73  | -10                                     | 32  |
| 7           | Mrs E G     | 48  | 4671              | -43                                      | 72  | -9                                      | 36  |
| 8           | Miss E MacD | 43  | 4423              | -24                                      | 72  | ±0                                      | 44  |
| 9           | Mrs G M     | 33  | 4434              | -27                                      | 65  | +7                                      | 27  |
| 10          | Mrs A J     | 33  | 4681              | -28                                      | 61  | -11                                     | 34  |
| 11          | Mrs M LeB   | 43  | 3532              | -24                                      | 58  | +15                                     | 41  |
| 12          | Mrs M B     | 57  | 1836              | -24                                      | 48  | -5                                      | 24  |
| 13          | Mrs A H     | 48  | 1807              | -22                                      | 46  | +16                                     | 27  |
| 14          | Mrs M H     | 35  | 4179              | -28                                      | 38  | +8                                      | 44  |
| 15          | Mrs D B     | 51  | 4339              | -25                                      | 34  | +17                                     | 21  |
| 16          | Mrs M M     | 53  | 4651              | -29                                      | 34  | +6                                      | 22  |
| 17          | Miss J W    | 47  | 2680              | -22                                      | 28  | ±0                                      | 31  |

The cell count was normal throughout

In most of the cases each figure represents the average of two or more determinations made on different days

\*The determinations were made on the first 2 to 3, cc. of fluid removed from the lumbar region

The protein content of the fluid obtained after withdrawing large quantities from the lumbar region (60 to 90 cc), was much greater than is found normally under these conditions, and was sometimes only slightly less than that of the first 2 cc removed This finding indicated that the protein content of cerebral fluid was greater than normal, a supposition that was supported by obtaining cistern

normal level In this respect, it is similar to a slow change in the myxedematous condition of the tissues

The change appears to persist as long as the metabolism is held at a normal level by the administration of thyroid extract

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|             |             |     |                   | <i>per cent of normal</i>                | <i>mgm per 100 cc</i>                     | <i>per cent of normal</i>               | <i>mgm per 100 cc</i>                     |
| 1           | Mr J G      | 53  | 4236              | -26                                      | 221                                       | -3                                      | 49  |
| 2           | Mrs J W     | 50  | 4224              | -21                                      | 129                                       | +2                                      | 58  |
| 3           | Mr H L      | 21  | 4302              | -34                                      | 111                                       | +19                                     | 30  |
| 4           | Mrs M V L   | 47  | 3984              | -17                                      | 93  | +23                                     | 32  |
| 5           | Mrs M B     | 30  | 4533              | -40                                      | 80  | -12                                     | 43  |
| 6           | Mrs L C     | 53  | 4532              | -46                                      | 73  | -10                                     | 32  |
| 7           | Mrs E G     | 48  | 4671              | -43                                      | 72  | -9                                      | 36  |
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| 10          | Mrs A J     | 33  | 4681              | -28                                      | 61  | -11                                     | 34  |
| 11          | Mrs M LeB   | 43  | 3532              | -24                                      | 58  | +15                                     | 41  |
| 12          | Mrs M B     | 57  | 1836              | -24                                      | 48  | -5                                      | 24  |
| 13          | Mrs A H     | 48  | 1807              | -22                                      | 46  | +16                                     | 27  |
| 14          | Mrs M H     | 35  | 4179              | -28                                      | 38  | +8                                      | 44  |
| 15          | Mrs D B     | 51  | 4339              | -25                                      | 34  | +17                                     | 21  |
| 16          | Mrs M M     | 53  | 4651              | -29                                      | 34  | +6                                      | 22  |
| 17          | Miss J W    | 47  | 2680              | -22                                      | 28  | ±0                                      | 31  |

The cell count was normal throughout

In most of the cases each figure represents the average of two or more determinations made on different days

\*The determinations were made on the first 2 to 3 cc. of fluid removed from the lumbar region

The protein content of the fluid obtained after withdrawing large quantities from the lumbar region (60 to 90 cc), was much greater than is found normally under these conditions, and was sometimes only slightly less than that of the first 2 cc removed This finding indicated that the protein content of cerebral fluid was greater than normal, a supposition that was supported by obtaining cistern

J G (case 1) had myxedema or a brain tumor. The latter diagnosis was seemingly corroborated by the finding of a high pressure as well as a high concentration of protein in the spinal fluid. His appearance was not characteristic of the full blown picture of myxedema. While the diagnosis was in doubt, similar spinal fluid findings were obtained for the first time in several cases of typical myxedema. Thyroid extract was, therefore, administered to J G and produced a well marked reduction in the concentration of protein, as well as a clinical cure.

The cause of the high protein concentration in the spinal fluid is uncertain. It is possibly related in some way to the storage of nitrogenous substances in myxedema (2) (3). It is of interest that an albuminuria is frequently present in this disease (2) (4) (5). This usually disappears or decreases markedly when thyroid is administered (5). The albuminuria and the high spinal fluid protein content may be, in part, manifestations of the same pathological condition, viz., an altered permeability of cell membranes throughout the body.

#### SUMMARY AND CONCLUSIONS

The concentration of protein in the spinal fluid is high in most cases of myxedema, and usually drops to within normal limits when thyroid extract is administered.

The high protein content both of cistern fluid and of fluid obtained after withdrawing large quantities from the lumbar region, indicates that the protein content of cerebral fluid is also high during the period of myxedema. This finding suggests that the fluid which comes through the choroid plexus may have a greater protein concentration than normal.

The knowledge that the concentration of protein in the spinal fluid is usually high in myxedema is of diagnostic value in rare instances in which this disease may be confused with brain tumor and chronic nephritis.

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TABLE 1  
*Recovery from diabetic acidosis with the aid of insulin, water, and carbohydrate, but without salt, or alkali*

| Blood serum        |           |      |                  |        |                  |                |             |               |            |                            |         |       |                |                  |            |
|--------------------|-----------|------|------------------|--------|------------------|----------------|-------------|---------------|------------|----------------------------|---------|-------|----------------|------------------|------------|
| Date               | Time      | BCI  | BHC <sub>2</sub> | pH     | Protein          |                | Lactic acid | Diacetic acid | Total base | Undetermined (ketone) acid | Glucose | N.P.N | Serum water    | Osmotic pressure |            |
|                    |           |      |                  |        | By refractometer | By Kjeldahl    |             |               |            |                            |         |       |                | Observed         | Calculated |
| Case 1 Eddie S     |           |      |                  |        |                  |                |             |               |            |                            |         |       |                |                  |            |
|                    |           | mM   | mM               |        | grams per cent   | grams per cent | mM          | mM            | mM         | mM                         | mM      | mM    | grams per cent | mM               | mM         |
| September 16, 1926 | 11 30 a m | 84.8 | 4.7              | 7.00   | 9.99             | 3.2            | 2.5         |               |            |                            | 488     | 37.8  |                | 351              |            |
| September 16, 1926 | 4 30 p m  | 79.2 | 6.0              | 7.13   | 9.13             |                |             |               |            |                            | 121     | 39.8  |                | 291              |            |
| September 16, 1926 | 9 30 p m  | 90.0 | 7.2              | 7.18   | 8.71             |                |             |               |            |                            | 78      | 46.2  |                | 285              |            |
| September 17, 1926 | 7 30 a m  | 90.0 | 14.2             | 7.23   | 8.49             |                |             |               |            |                            | 91      | 41.8  |                |                  |            |
| September 17, 1926 | 5 00 p m  | 87.0 | 14.0             | 7.38   | 8.28             |                |             |               |            |                            | 70      | 42.0  |                |                  |            |
| September 18, 1926 | 8 00 a m  | 80.0 | 15.8             | 7.35   | 7.85             |                |             |               |            |                            | 259     | 66.0  |                |                  |            |
| September 21, 1926 | 8 00 a m  | 80.4 | 21.4             | 7.38   | 7.63             |                |             |               |            |                            | 430     | 50.0  |                |                  |            |
| Case 2 Billy R     |           |      |                  |        |                  |                |             |               |            |                            |         |       |                |                  |            |
|                    |           | mM   | mM               |        | grams per cent   | grams per cent | mM          | mM            | mM         | mM                         | mM      | mM    | grams per cent | mM               | mM         |
| June 3, 1926       | 11 30 a m | 92.0 | 6.2              | 7.17   | 9.99             |                |             |               |            |                            | 516     | 52.2  |                |                  |            |
| June 3, 1926       | 4 00 p m  | 91.2 | 7.7              | 7.22   | 9.77             |                |             |               |            |                            | 380     |       |                |                  |            |
| June 3, 1926       | 9 00 p m  |      |                  |        |                  |                |             |               |            |                            | 182     |       |                |                  |            |
| June 4, 1926       | 8 45 a m  | 95.2 | 19.1             | (7.35) | 8.81             | (3.0)          | (2.0)       |               | 138        | 1.0                        | 112     | 46.2  |                |                  |            |
| June 5, 1926       | 8 45 a m  | 86.0 | 17.8             |        | 8.06             |                |             |               |            |                            | 349     | 36.6  |                |                  |            |





TABLE 2  
*Recovery from diabetic acidosis with the aid of insulin, water, carbohydrate and Ringer's solution, but without alkali*

| Blood serum      |           |       |                   |      |                  |             |                    |              |                |            |                            |         |       |                |                  |            |  |
|------------------|-----------|-------|-------------------|------|------------------|-------------|--------------------|--------------|----------------|------------|----------------------------|---------|-------|----------------|------------------|------------|--|
| Date             | Time      | BCl   | BHCO <sub>3</sub> | pH   | Protein          |             | B HPO <sub>4</sub> | Lactic acid* | Diabetic acid* | Total base | Undetermined (ketone acid) | Glucose | N P N | Serum water    | Osmotic pressure |            |  |
|                  |           |       |                   |      | By refractometer | By Kjeldahl |                    |              |                |            |                            |         |       |                | Observed         | Calculated |  |
| Case 4 Loretta B |           |       |                   |      |                  |             |                    |              |                |            |                            |         |       |                |                  |            |  |
| January 24, 1927 | 11 45 a m | 95 0  | 12 9 (7 30)       | 8 92 | grams per cent   | mM          | mM                 | mM           | mM             | mM         | mM                         | mM      | mM    | grams per cent | mM               | mM         |  |
| January 25, 1927 | 9 00 a m  | 96 5  | 5 4 (7 20)        | 9 13 |                  | 3 5         | (2 0)              | 5 1          | 146            | 15         | 248                        | 31 7    |       |                |                  | 303        |  |
| January 25, 1927 | 2 00 p m  |       |                   |      |                  |             | (2 0)              | 7 4          |                |            | 386                        | 29 6    |       |                |                  |            |  |
| January 26, 1927 | 9 00 a m  | 98 7  | 5 9 (7 20)        | 9 99 |                  | 3 3         | (2 0)              | 8 0          |                |            | 457                        | 36 8    |       |                |                  |            |  |
| January 26, 1927 | 2 00 p m  | 102 0 | 7 0 7 25          | 9 77 |                  | 3 2         | (2 0)              | 8 4          | 147            | 14         | 300                        | 40 0    |       |                |                  | 309        |  |
| January 27, 1927 | 9 00 a m  | 101 0 | 10 8 7 30         | 7 85 |                  | 3 0         | (2 0)              | 6 5          | 143            | 11         | 295                        | 32 8    |       |                |                  | 302        |  |
| January 28, 1927 | 9 00 a m  | 96 0  | 13 2 7 34         | 7 63 |                  | (3 0)       | (2 0)              | 5 8          | 143            | 13         | 297                        | 34 4    |       |                |                  | 300        |  |
| January 29, 1927 | 9 30 a m  |       |                   | 7 63 |                  |             | (2 0)              | 5 0          |                |            | 500                        |         |       |                |                  |            |  |
| February 4, 1927 | 9 00 a m  | 95 0  | 24 9 7 49         | 6 55 |                  | (3 0)       | 1 8 (0)            |              | 146            | 6          | 282                        | 25 0    |       |                |                  | 301        |  |
| February 7, 1927 | 9 00 a m  | 96 0  | 25 4 7 49         | 6 55 |                  | (3 0)       | 1 4 (0)            |              | 144            | 4          | 56                         | (25 0)  |       |                |                  | 274        |  |
| Case 1 Eddie S   |           |       |                   |      |                  |             |                    |              |                |            |                            |         |       |                |                  |            |  |
| April 15, 1927   | 11 00 a m | 92 3  | 5 3 7 07          | 11 8 |                  | 4 6         | 5 6                | 4 5          | 141            | 10         | 734                        | 45 0    |       |                | 309              | 325        |  |
| April 16, 1927   | 9 00 a m  | 95 3  | 16 2 7 35         | 8 06 |                  | 2 5         | 2 1                | 2 2          | 135            | 3          | 29                         | 38 0    |       |                |                  | 273        |  |

( ) Assumed values

\* Determined together in Case 4

TABLE 2

*Recovery from diabetic acidosis with the aid of insulin, water, carbohydrate and Ringer's solution, but without alkali*

| Blood serum      |           |       |                  |        |                  |                |                    |              |                |            |                            |         |        |                |                  |            |
|------------------|-----------|-------|------------------|--------|------------------|----------------|--------------------|--------------|----------------|------------|----------------------------|---------|--------|----------------|------------------|------------|
| Date             | Time      | BCl   | BHC <sub>2</sub> | pH     | Protein          |                | B HPO <sub>4</sub> | Lactic acid* | Diabetic acid* | Total base | Undetermined (ketone) acid | Glucose | N P N  | Serum water    | Osmotic pressure |            |
|                  |           |       |                  |        | By refractometer | By Kjeldahl    |                    |              |                |            |                            |         |        |                | Observed         | Calculated |
| Case 4 Loretta B |           |       |                  |        |                  |                |                    |              |                |            |                            |         |        |                |                  |            |
| January 24, 1927 | 11 45 a m | mM    | mM               |        | grams per cent   | grams per cent | mM                 | mM           | mM             | mM         | mM                         | mM      | mM     | grams per cent | mM               | mM         |
| January 25, 1927 | 9 00 a m  | 95 0  | 12 9             | (7 30) | 8 92             | 3 5            | 3 5                | (2 0)        | 5 1            | 146        | 15                         | 248     | 31 7   |                |                  | 303        |
| January 25, 1927 | 2 00 p m  | 96 5  | 5 4              | (7 20) | 9 13             |                |                    | (2 0)        | 7 4            |            |                            | 386     | 29 6   |                |                  |            |
| January 26, 1927 | 9 00 a m  | 98 7  | 5 9              | (7 20) | 9 99             | 3 3            | 3 3                | (2 0)        | 8 0            |            |                            | 457     | 36 8   |                |                  |            |
| January 26, 1927 | 2 00 p m  | 102 0 | 7 0              | 7 25   | 9 77             | 3 2            | 3 2                | (2 0)        | 8 4            | 147        | 14                         | 300     | 40 0   |                |                  | 309        |
| January 27, 1927 | 9 00 a m  | 101 0 | 10 8             | 7 30   | 7 85             | 3 0            | 3 0                | (2 0)        | 6 5            | 143        | 11                         | 295     | 32 8   |                |                  | 302        |
| January 28, 1927 | 9 00 a m  | 96 0  | 13 2             | 7 34   | 7 63             | (3 0)          | (3 0)              | (2 0)        | 5 8            | 143        | 13                         | 297     | 34 4   |                |                  | 300        |
| January 29, 1927 | 9 30 a m  |       |                  |        | 7 63             |                |                    | (2 0)        | 5 0            |            |                            | 500     |        |                |                  |            |
| February 4, 1927 | 9 00 a m  | 95 0  | 24 9             | 7 49   | 6 55             | (3 0)          | (3 0)              | 1 8          | (0)            | 146        | 6                          | 282     | 25 0   |                |                  | 301        |
| February 7, 1927 | 9 00 a m  | 96 0  | 25 4             | 7 49   | 6 55             | (3 0)          | (3 0)              | 1 4          | (0)            | 144        | 4                          | 56      | (25 0) |                |                  | 274        |
| Case 1 Eddie S   |           |       |                  |        |                  |                |                    |              |                |            |                            |         |        |                |                  |            |
| April 15, 1927   | 11 00 a m | 92 3  | 5 3              | 7 07   | 11 8             | 4 6            | 4 6                | 5 6          | 4 5            | 141        | 10                         | 734     | 45 0   |                | 309              | 325        |
| April 16, 1927   | 9 00 a m  | 95 3  | 16 2             | 7 35   | 8 06             | 2 5            | 2 5                | 2 1          | 2 2            | 135        | 3                          | 29      | 38 0   |                |                  | 273        |

( ) Assumed values

\* Determined together in Case 4





least a roughly quantitative fashion in the same manner that lactic acid was determined <sup>1</sup>

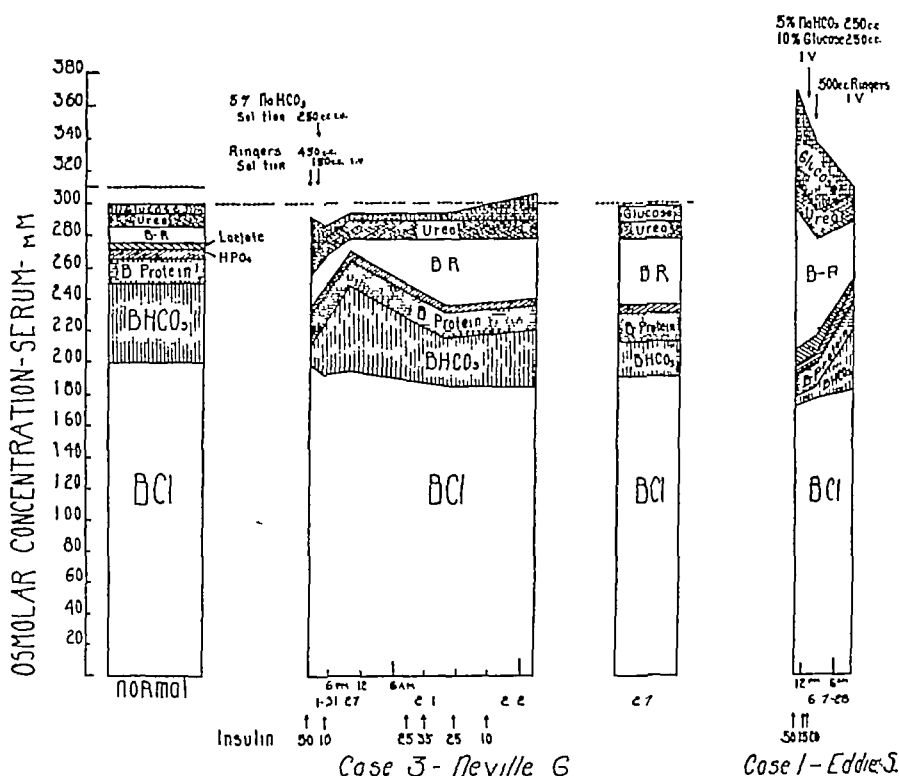


CHART 3 THE OSMOLAR ELECTROLYTE AND NON-ELECTROLYTE COMPOSITION OF THE PLASMA IN SEVERE DIABETIC ACIDOSIS, AND CHANGES TAKING PLACE AS A RESULT OF THE ADMINISTRATION OF WATER, INSULIN, CARBOHYDRATE, SALT SOLUTION AND ALKALI

In estimating the concentration of the total ketone acids, the sum of the principal normal acids ( $\text{Cl}' + \text{HCO}_3' + \text{protein}' + \text{HPO}_4''$

<sup>1</sup> By titrating as rapidly as possible the bisulfite freed from combination with acetaldehyde and acetone, lactic acid and diacetic acid together were determined. Lactic acid alone was then determined in the usual manner after preliminary distillation in acid solution of preformed acetone and diacetic acid, the distillate being caught in Scott-Wilson reagent and furnishing a rough check on the value obtained by titration difference.



April 16, 1927 6 00 a m Insulin 15 units subcutaneously

Admission of April 3, 1928 (table 3)

April 3, 1928

11 45 a m Insulin 40 units, intravenously

11 45 a m Insulin, 40 units, subcutaneously

11 45 a m 7.5 per cent glucose solution, 400 cc, intravenously

11 45 a m Ringer's solution, 400 cc, intravenously

11 45 a m 5 per cent sodium bicarbonate solution 500 cc, intravenously

3 00 p m Insulin, 50 units, subcutaneously

4 00 p m Ringer's solution by Murphy drip per rectum

9 00 p m Insulin 15 units subcutaneously

April 4, 1928

3 00 a m Insulin, 15 units, subcutaneously

9 00 a m Meal P 20, F 50, CH 20

9 00 a m Insulin 20 units, subcutaneously

12 30 p m Meal as above

12 30 p m Insulin 15 units subcutaneously

6 00 p m Meal as above

6 00 p m Insulin 15 units, subcutaneously

April 5, 1928 Meals and insulin as on April 4, 1928

Admission of June 6, 1928 (table 3)

June 6, 1928

11 45 p m Insulin 50 units intravenously

1 00 a m 500 cc 5 per cent Glucose solution containing 12.5 grams  
NaHCO<sub>3</sub> and 15 units insulin, intravenously

June 7, 1928

1 30 a m Ringer's solution 400 cc intravenously

1 30 a m Insulin 20 units subcutaneously

9 00 a m Previous diet and insulin dosage resumed

*Case 2* Billie R. This patient developed symptoms of diabetes mellitus in January, 1924, when 8 years of age. During hospital admission in February, 1924, he was found to be a mild diabetic, showing no hyperglycemia on the usual diabetic diet without insulin. After discharge from the hospital, dietary indiscretions were frequent, and gradually carbohydrate tolerance was lost, and daily insulin administration became necessary. As punishment for one such lapse on June 1, 1926, he was put to bed without supper or insulin. The next morning he complained of abdominal pain, felt nauseated and vomited. Because he would not eat breakfast, insulin was again withheld. Abdominal pain and nausea persisted, hyperpnea and drowsiness were noted and he was then brought to the hospital. As in Case 1, leucocytosis of 40,000 without fever, was noted, and all symptoms disappeared when recovery from acidosis occurred (table 2).

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9 00 p m Insulin 15 units subcutaneously

April 4, 1928

3 00 a m Insulin, 15 units, subcutaneously

9 00 a m Meal *P* 20, *F* 50, *CH* 20

9 00 a m Insulin 20 units, subcutaneously

12 30 p m Meal as above

12 30 p m Insulin 15 units subcutaneously

6 00 p m Meal as above

6 00 p m Insulin 15 units, subcutaneously

April 5, 1928 Meals and insulin as on April 4, 1928

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January 25, 1927

9 00 a m Insulin 50 units intravenously Ringer's solution per rectum by Murphy drip

3 25 p.m Insulin 35 units subcutaneously Orange juice 200 cc 4 per cent glucose per rectum as Murphy drip Orange juice 200 cc

8 00 p m Insulin 15 units subcutaneously

January 26, 1927

2 00 a m Insulin 15 units subcutaneously

9 00 a m 5 per cent glucose 1000 cc intravenously

9 30 a m Insulin 50 units intravenously

10 45 a m Insulin 50 units subcutaneously

12 45 p m Insulin 50 units subcutaneously

11 00 p m Ringer's solution 500 cc subcutaneously

January 27, 1927

Insulin 125 units subcutaneously

Ringer's solution 500 cc subcutaneously

Regular diet

January 28, 1927 Insulin 110 units, subcutaneously, with full diet

*Case 5* Frances H Diabetic symptoms were first noted in December, 1923, when he was 9 years of age Shortly afterwards he was admitted to the hospital, where he was found normal except for moderately severe diabetes After a temporary improvement, his carbohydrate tolerance again diminished On March 1, 1927, he was admitted with alkalosis, following too vigorous treatment with alkali and insulin administered by his family physician Proper diet and insulin routine were frequently interrupted and he was admitted to the hospital again on December 5, 1927, with moderately severe acidosis (table 1) Therapy was as follows

December 5, 1927

10.20 p m 10 per cent glucose 500 cc intravenously Insulin 40 units intravenously

11 00 p m Insulin 40 units, subcutaneously

December 6, 1927 Usual diet and insulin

*Case 6* James Y Diabetic symptoms were first noticed in June, 1926, when he was 13 years of age After hospital admission, he was found normal except for moderately severe diabetes and was given an adequate diet and insulin dosage He did well in the hospital and after discharge until he developed a respiratory infection, which resulted in severe acidosis on December 29, 1927 Therapy at that time was as follows

December 29, 1927

5 30 p m Insulin 35 units subcutaneously

9 00 p m 10 per cent glucose 250 cc intravenously

9 00 p m Insulin 13 units, intravenously

January 25, 1927

9 00 a m Insulin 50 units intravenously Ringer's solution per rectum by Murphy drip

3 25 p.m Insulin 35 units subcutaneously Orange juice 200 cc 4 per cent glucose per rectum as Murphy drip Orange juice 200 cc

8 00 p m Insulin 15 units subcutaneously

January 26, 1927

2 00 a m Insulin 15 units subcutaneously

9 00 a m 5 per cent glucose 1000 cc intravenously

9 30 a m Insulin 50 units intravenously

10 45 a m Insulin 50 units subcutaneously

12 45 p m Insulin 50 units subcutaneously

11 00 p m Ringer's solution 500 cc subcutaneously

January 27, 1927

Insulin 125 units subcutaneously

Ringer's solution 500 cc subcutaneously

Regular diet

January 28, 1927 Insulin 110 units, subcutaneously, with full diet

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In the more severe cases,  $\text{BHCO}_3$  may be but 5 mM (corresponding to about 12 vols per cent  $\text{CO}_2$  content) and the pH may be 7.00 or less. In most instances, increase in ketone acids more than accounts for such diminution of the bicarbonate ion. In one case, however (Case 3, table 3) there was noted a 17.0 mM decrease in  $\text{BHCO}_3$  with but an indicated 9.0 mM increase in ketone acid.

Of the remaining acids, chloride is most regularly affected. Its concentration is always below normal, sometimes by as much as 20 mM. Occasionally lactic acid is significantly increased, as in Case 1 on April 3, 1928 (table 3). Phosphoric acid concentration tends to be elevated slightly, but such elevation is not significant from the standpoint of its base-binding capacity. Increase in protein concentration, although sometimes very marked, usually increases but little the base bound to protein because of the fall in pH which accompanies the plasma concentration.

From the osmolar viewpoint, we note a reduction in total electrolyte concentration, with an increase in glucose concentration sufficient to maintain a normal or a high osmotic pressure. The initially highest observed total osmolar concentration as indicated by the freezing point depression was 394 mM and occurred in Case 1 on April 3, 1928 (table 3). In this instance the theoretical osmolar concentration was 354 mM, 84 per cent of which was contributed by electrolyte. The least depression of the freezing point (309 mM) was noted in case 1 on April 15, 1927 (table 2). In this instance the theoretical osmolar concentration was 325 mM, electrolyte accounting for 82.2 per cent of it.

*Recovery resulting from the administration of water, insulin and carbohydrate*

The results of therapy as indicated above can be seen in table 1 and chart 1<sup>2</sup>. The outstanding feature is the rapid disappearance of blood sugar, frequently sufficient, even despite carbohydrate administration, to produce marked hypoglycemia, without the simultaneous return of  $\text{BHCO}_3$  to anywhere near its normal concentration. Thus in Case 1 on September 16, 1927 ten hours after the beginning of

<sup>2</sup> In constructing this chart, total base values, equivalent to the average found on other occasions, were assumed.

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ance with the Donnan principle of ionic and osmotic equilibrium, as shown by Van Slyke and his co-workers (4) to occur, but also into the fixed tissue cells, as suggested recently by Peters, returning to the plasma later as the hydrogen ion concentration of the cells diminished.

It is of interest to note, however, that ultimately chloride *aids* in the recovery of plasma  $\text{BHCO}_3$ . In Case 1, for instance, it may be noted that as  $\text{BHCO}_3$  increased from 14.2 mM on September 17, 1926 to 21.4 mM on September 21, 1926, BCl diminished from 90.0 to 80.4 mM. This diminution of plasma chloride occurred after re-establishment of urinary secretion and during a time in which the hydrogen ion concentration of the plasma was diminishing. It seems reasonable to assume, therefore, that when urinary secretion is re-established,  $\text{BHCO}_3$  is supported by excretion of ammonium chloride into the urine.

From such data as shown in table 1, therefore, we may conclude that administration only of water and insulin, with or without carbohydrate, restores but very slowly the  $\text{BHCO}_3$  of the plasma, and therefore of the body fluids in general, the probable explanation being that as the hydrogen ion concentration of the fixed tissue cell decreases, the cell proteins claim base liberated from organic acid and chloride, the latter shifting into the plasma and claiming base originally held by organic acid, which otherwise might have combined with carbonic acid. Later chloride may be further shifted into the urine, bound to ammonia and thus release base for combination with carbonic acid.

With these points in mind, it should be of interest to note whether or not *salt solution* administration along with insulin, water, and carbohydrate, by causing an earlier and more intensive secretion of ammonium chloride into the urine causes a speedier restoration of plasma  $\text{BHCO}_3$ .

#### *The effect of salt administration*

In Case 4 (table 2, chart 2) on January 24, 1927, during the first 48 hours of treatment consisting of administration of water, insulin, carbohydrate and Ringer's solution, "acidosis" actually became more marked, the plasma  $\text{BHCO}_3$  falling from 12.9 to 5.9 mM. During this interval, despite considerable insulin, little change in the blood sugar level was noted, and total organic acid concentration remained

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of ketone acid had occurred,  $\text{BHCO}_3$  reached a high normal value, 26.1 mM. In addition to this rapid and complete relief from acidosis, alkali administration had also the effect of diluting the plasma very rapidly, if we can judge from the refractometric values of protein.

In Case 1, on June 6, 1928, extreme acidosis was present,  $\text{BHCO}_3$  was but 3.0 mM and pH was less than 7.00. Despite immediate administration of insulin intravenously, no improvement was noted in two and one-half hours. Alkali was then given, and there followed immediate clinical improvement and in seven and one-half hours plasma  $\text{BHCO}_3$  was 22.9 mM and pH 7.43.

Similar almost perfect chemical restitution of the plasma in 12 to 24 hours by means of combined insulin and alkali therapy was noted earlier in our experience (5). At that time, however, we were not as convinced as we are at present of the necessity of alkali in extreme cases of diabetic acidosis, and feared the development later of alkalosis. It is very doubtful whether moderate alkalosis does any more harm than moderate acidosis, and certainly extreme alkalosis has been observed in cases of pyloric stenosis (6) with little in the way of alarming symptoms. Similarly marked increase in plasma  $\text{BHCO}_3$  developed in Case 1 on April 4, 1928, after combined insulin and alkali treatment without symptoms or apparent harm. If tetany had occurred, we feel that it could easily have been controlled by inhalation of carbon dioxide and administration intravenously of calcium chloride. We quite agree, however, that marked alkalosis should be avoided if possible and critical study of those cases who received alkali and developed alkalosis is indicated.

Such a study, including observation of both blood and urine will be reserved for a later paper.

In the meantime, however, we feel that cases of diabetic acidosis as severe as the cases described in this paper will be greatly benefited if, in addition to the usual water, insulin, carbohydrate and salt administration, alkali equivalent to one-fourth of that normally present in the body fluids is also administered. For calculating such a dosage it is assumed that the body fluid comprises two-thirds of the body weight, and at its normal pH contains 3.0 grams of sodium bicarbonate per liter.

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The data reported herein are in terms of the percentage of weight, surface, and calories-per-hour above the corresponding values for persons of the same age and height, but of ideal weight.

#### METHODS

The observations reported here were made on eight obese women normal except for their excess weight. They were being reduced by dietary measures alone over periods varying from a few days to twenty weeks. All of them were so

TABLE 1  
*Basal heat production in the obese*

|                      | Number of cases | Average calories per hour | Average basal metabolic rate |
|----------------------|-----------------|---------------------------|------------------------------|
|                      |                 |                           | <i>per cent</i>              |
| Means (4)            | 10              | 81                        | 0                            |
| Strouse and Wang (5) | 10              | 74                        | +1                           |
| Present series       | 7               | 73                        | -3                           |

intelligent and reliable that their adherence to the prescribed routine was not to be doubted. In this series, there were three completed cases, three only partly reduced and two cases which have been observed for less than one month. All of these patients carried on their usual activities throughout the dietary period.

The diet was calculated on the basis of 1 gram of protein and 25 calories per kilogram of ideal weight. Utilizing a FA/G ratio of 1.5, the grams of protein, carbohydrate, and fat were determined. From these figures, the menu was made up including the protein and carbohydrate and omitting as much of the fat as possible. This made possible diets with 600 to 650 calories total intake which was equivalent to 6 calories per kilogram actual weight in some of the patients studied.

Basal metabolism determinations were done at intervals varying from a few days to two weeks using standard technique. The Tissot apparatus was used and gas samples were analyzed in duplicate.

The current insurance tables were used as standards of ideal weight (16). Surface area was calculated from the Boothby-Sandiford logarithmic chart (17).

A study of nitrogen balance in one patient of this series showed that the diet

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given kept her approximately in nitrogen equilibrium. This observation and investigations in another series of cases to be reported later give reason to believe that all the patients maintained an approximate nitrogen balance during the period of dieting.

### OBSERVATIONS

The data presented are based upon 70 observations, 53 of which were made on the 5 cases which are considered as "reduced." The figures showing the status prior to dieting are the lowest values obtained before the diets began. There is no evidence that the determinations were in any way unusual.

A summary of our data appears in table 2. The averages of the initial data represent observations on all 7 cases. For comparison

TABLE 3  
*Influence of diet on calories per hour*

| Case number | Outset | First month | Second month | Third month | Fourth month | Fifth month |
|-------------|--------|-------------|--------------|-------------|--------------|-------------|
| 1           | 69     | 65          | 63           | 62          | 53           | 52          |
| 2           | 70     | 68          | 63           | 64          | 63           |             |
| 3           | 72     | 75          | 73           | 76          | 72           | 69          |
| 4           | 74     | 69          | 64           | 65          | 62           | 62          |
| 5           | 70     | 66          | 58           | 60          |              |             |
| Average     | 71     | 66          | 64           | 65          | 62           | 61          |

with the figures after reduction, the averages of the initial values for the 5 reduced cases are tabulated separately. The influence of weight reduction is shown in the second part of the table. These figures describe the metabolic status of each patient on the day of her last examination after the designated period of dietary restriction.

The influence of dietary measures on the total calories per hour is indicated in table 3 which shows the average values for all determinations made during the given months.

Eight observations have been made upon a woman 52 years of age who was only 25 per cent overweight at the outset. Her surface was 11 per cent increased and the calories, 4 per cent above the ideal normal. In 6 weeks, she was reduced to 7 per cent excess weight with corresponding surface but no significant change in total

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Relatively large weight changes amounting to 2 to 4 pounds a day are commonly met with in the obese. This phenomenon is apparently explained by the variable capacity of fat deposits for water storage, a conception which is supported by Lauter's (3) statement that the water content of human fat may vary from 8 to 70 per cent. These large water shifts give rise to a plateau-and-step type of weight curve during reduction which has been mentioned by Newburgh (4) and others and which we have repeatedly observed. We do not, however, feel that this factor materially influences our data.

That a loss of fat tissue rather than a shifting water balance is responsible for the observed weight change is suggested by the following calculation. "Gross" calories ingested are used instead of "net" calories in view of the relatively small energy fraction supplied by food. The average basal calories per hour (table 3) plus 20 per cent is used as a measure of the total energy requirement (Mason (7)). Following the suggestion of DuBois (9) after Bozenraad, we estimate that 75 kgm of fatty tissue have 65 kgm of fat or 87 per cent fat.

Basal calories per hour = 65

Basal calories per 24 hours = 1,560

Daily energy requirement—basal plus 20 per cent = 1870 calories

Average calories in diet = 620

1870 — 620 equals 1250 calories from fat

1250/9.3 equals 134 grams of fat equals  $134 \times 75/65$  or 155 grams of fatty tissue per day

Average duration = 17 weeks or 119 days

$\frac{155 \times 119 \times 2.2}{1000}$  equals 40.6 pounds

Weight loss observed = 41 pounds

On the basis indicated above, we have, therefore, accounted for nearly all of the gross observed weight loss.

### *Surface changes*

The significance of numerical values for body surface and surface changes depends upon the reliability of the method of estimation. We have used tables based upon the DuBois formula which seems to be generally credited as the best available approximation even for the obese (3, 4, 10).

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*Effect of weight reduction on energy exchange*

If an obese patient may have a basal caloric requirement 30 per cent in excess of normal, it becomes important to know what happens to this excess when the weight is reduced. If the basal calories do not change, the reduced person will have a metabolism comparable to that of a seriously toxic thyroid patient. There is some evidence to indicate that the production of thyrotoxic symptoms by simple dietary reduction is not an impossibility (unpublished case).

In reviewing these data, the limits of normal variations in metabolism must be kept in mind. Harris and Benedict (13) published data in 1921 showing the extreme variations of metabolism in a given person

TABLE 4  
*Excess of weight, surface and energy in the obese*

|                  | Number of cases | Age | Weight |          |                 | Surface |          |                 | Total basal calories per hour |          |                 |
|------------------|-----------------|-----|--------|----------|-----------------|---------|----------|-----------------|-------------------------------|----------|-----------------|
|                  |                 |     | Ideal  | Observed | Excess          | Ideal   | Observed | Excess          | Ideal                         | Observed | Excess          |
|                  |                 |     |        |          |                 |         |          |                 |                               |          |                 |
|                  |                 |     |        |          | <i>per cent</i> |         |          | <i>per cent</i> |                               |          | <i>per cent</i> |
| Means            | 10              | 37  | 140    | 253      | 80              | 1 69    | 2 17     | 28              | 62                            | 81       | 30              |
| Strouse and Wang | 10              | 27  | 125    | 207      | 66              | 1 57    | 1 95     | 24              | 59                            | 74       | 25              |
| Present series   | 7               | 37  | 129    | 238      | 83              | 1 59    | 2 06     | 29              | 58                            | 73       | 26              |

Over a period of two years, a 14 per cent variation might be noted. However, in a series of cases studied from one to three months, the coefficients of variation were around 4 per cent of the average metabolism. DuBois (9) thinks that the variations in metabolism are smaller than the possible errors of the determinations.

Acidosis causes an elevation in metabolism. Mason (7) and others have found no evidence of clinical acidosis after the first few days of diet restriction in spite of the presence of acetone bodies in the urine. This absence of clinical acidosis is in accord with our own experience.

The average of our 5 cases shows a diminution of basal energy requirements of 240 calories or 14 per cent of the initial value. Expressed in terms of the physiological status, these cases, which initially were metabolising 23 per cent in excess of normal, have

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Can this conclusion in regard to weight reduction in the obese apply to loss of weight in a normal person? Is the physiological reaction the same? For answer one might refer to the well-known work on this question of Benedict (14) and his collaborators which is briefly summarized below. It is useful to distinguish three degrees of undernutrition, acute and chronic undernutrition, and starvation. For comparison with our data one example of each type is taken from Benedict. In tables 5 and 6, the figures for Squad A and B are taken from Lusk's (15) review of Benedict's work, and, in consequence, certain values differ very slightly from the original data of Benedict.

In comparing ours with those of Benedict, it must be emphasized that his cases were healthy active males while our patients were

TABLE 6  
*Rates of change of weight, surface and energy*

| Group | Type       | Subject | I               | II              | III                 | IV                                   | V                                     |
|-------|------------|---------|-----------------|-----------------|---------------------|--------------------------------------|---------------------------------------|
|       |            |         | Weight loss     | Surface loss    | Basal calories loss | Ratio<br>Calorie loss<br>Weight loss | Ratio<br>Calorie loss<br>Surface loss |
|       |            |         | <i>per cent</i> | <i>per cent</i> | <i>per cent</i>     |                                      |                                       |
| I     | Acute      | Squad B | 6.5             | <1.0            | 32.0                | 4.9                                  | 32.0+                                 |
| II    | Starvation | Leveran | 17.0            | 5.0             | 30.0                | 1.7                                  | 6.0                                   |
| III   | Chronic    | Squad A | 8.5             | 3.3             | 19.0                | 2.2                                  | 5.9                                   |
| IV    | Obese      |         | 18.0            | 8.5             | 14.0                | 0.77                                 | 1.6                                   |

obese females. They had at the outset physiologically normal basal metabolism, while that of this series was elevated 23 per cent.

In regard to weight loss, none of the undernutrition cases approaches the magnitude of loss of our patients. On a percentage basis, the starvation case lost a comparable amount.

Clinically, the response in the two groups was entirely different, the undernourished groups became less ambitious, less energetic, tried to conserve all possible energy. They were depressed, irritable, and unstable. In contrast to this, the obese cases showed consistently more initiative, had a desire to do things, and felt in all respects better than for years previously.

The physiological reaction is different in the different groups of cases. The first two dropped 30 per cent of their calories in three

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Clinically, the response in the two groups was entirely different, the undernourished groups became less ambitious, less energetic, tried to conserve all possible energy. They were depressed, irritable, and unstable. In contrast to this, the obese cases showed consistently more initiative, had a desire to do things, and felt in all respects better than for years previously.

The physiological reaction is different in the different groups of cases. The first two dropped 30 per cent of their calories in three

very much less in proportion to limitation of diet and weight loss and is only a return toward normal, never beyond, of an initially elevated rate. These observations, and the clinical differences in the two groups of cases, permit the conclusion that our patients were not physiologically undernourished. The obese, when on a limited diet—with sufficient protein—do not seem to require the protective depression of the energy exchange which Lusk describes in connection with the above groups of undernourished.

No difference in quality of reaction was noted in the response of the so-called "endocrine" obesity patients and the "over-eating" cases. There appears to be a difference in quantity of reaction due, perhaps, to the tendency of the former type to approach the theoretical basal metabolism more rapidly in proportion to weight loss than in the second type. The weight loss continues in all cases to be directly proportional to the degree of deficiency of exogenous calories.

#### CONCLUSIONS

- 1 The energy exchange in the obese, when compared to what would be normal for them, if on proper weight, is increased.

- 2 This increase in energy exchange is of the same magnitude as the surface area increase beyond that normal for them.

- 3 When obese patients are reduced by dietary measures alone, the energy exchange diminishes proportionally much more than the weight, or surface area.

- 4 In spite of this drop in basal calories the metabolism never goes below limits normal for proper weight.

- 5 This observation contrasts strikingly with the extreme energy economy in the individual of normal weight who is reducing by diet, as is shown by a comparison with Benedict's figures.

- 6 There is, therefore, no evidence of an energy economy in the obese.

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- 1 Evans, F. A., *Proc. Am. Chm. and Clin. Assn.*, 1928. Treatment of Simple Obesity by Dietary Measures Alone.
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through glucose, which it has been shown requires insulin in its metabolism. It has been shown that if the triose normally appears in the blood the amount must be exceedingly minute (5), that, when administered, it disappears from the blood coincident with the appearance of extra glucose (6, 7), that it cures insulin hypoglycemia (6), which only certain hexoses can do, that when administered to depancreatized dogs on a fixed diet and insulin, the same amount of glucose is excreted in the urine as when glucose itself is fed (7), that the fasting depancreatized dog excretes the same amount of extra glucose as is equivalent to the weight of triose fed (7), that the respiratory quotient of a fasting depancreatized dog is not affected by the administration of the triose (7), and that in the eviscerated animal the dihydroxyacetone does not cure the hypoglycemia nor disappear from the blood as does glucose but, in the absence of the liver, remains unchanged, and that most of the substance can be obtained from the muscles as the unchanged triose (9).

These investigations, however, did not include any evidence as to the behavior of the total metabolism of a fasting *normal* dog when given glucose or dihydroxyacetone. The protocols later presented are of interest in supplying this information under experimental conditions, which have not been quite duplicated in man and from which further deductions may be drawn. These observations were undertaken in the period November 1 to 16, 1926. From the December number of the *Proceedings of the Society for Experimental Biology and Medicine* we learned that Himwich, Rose and Malev (10) had presented a preliminary note on a somewhat similar experiment on December 15, 1926. Since, so far as we know, no more extensive report by these authors has appeared in the past year it seems desirable to place these observations on record.

Himwich, Rose and Malev, using a trained dog, injected 10 grams of glucose or dihydroxyacetone dissolved in warm water subcutaneously and collected the expired air at short intervals through a leakproof mask into a spirometer whence samples were collected over mercury and analyzed by the Haldane-Henderson apparatus. Prompt increases in the respiratory quotient occurred, the latter rising, in fact, over 1.0 in all experiments with dihydroxyacetone and in one case to 1.31. In the glucose experiments the respiratory quotient increased,

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total gaseous exchange in any one period and, therefore, figures on heat production per hour have been omitted. It should also be stated that the behavior of the animals was very satisfactory. The

TABLE 1

| Period           | O <sub>2</sub> absorp-<br>tion | CO <sub>2</sub> elimina-<br>tion | R Q               | O <sub>2</sub> per kgm<br>hour | Remarks                                       |
|------------------|--------------------------------|----------------------------------|-------------------|--------------------------------|---|
| November 1, 1926 | Dog A                          | White wire-haired terrier        | Weight 6120 grams | Last                           | previous feeding October 30, 9 00 a m         |
| 8 55- 9 55 a m   | 4,566                          | 3,485                            | 0 76              | 746                            | Quiet   |
| 9 55-10 55 a m   | 4,192                          | 3,073                            | 0 733             | 685                            | Very quiet<br>Slight movements<br>Very quiet  |
| 11 05 a m        |                                |                                  |                   |                                | Electric power off                            |
| 11 50 a m        |                                |                                  |                   |                                | 25 grams glucose in 150 cc<br>water           |
| 12 15- 1 15 p m  | 4,572                          | 3,719                            | 0 814             | 747                            | Very quiet<br>Sitting up Quiet<br>3 movements |
| 1 15- 2 15 p m   | 4,150                          | 3,595                            | 0 866             | 678                            | Occasional movement                           |
| 2 15- 3 15 p m   | 3 644                          | 3 078                            | 0 845             | 595                            | Quiet<br>Dog fed 4 00 p m                     |
| November 3, 1926 | Same dog                       | Weight 6000 grams                | Last              | previous feeding               | November 1, 4 00 p m                          |
| 8 35- 9 35 a.m   | 4,563                          | 3,340                            | 0 732             | 760                            | Quiet   |
| 9 35-10 35 a m   | 4,074                          | 3,144                            | 0 772             | 679                            | Very quiet<br>Very quiet                      |
| 10 45 a m        |                                |                                  |                   |                                | 25 grams dihydroxyace-<br>tone                |
| 11 10-12 10 p m  | 4,032                          | 3,969                            | 0 984             | 672                            | Very quiet                                    |
| 12 10- 1 10 p m  | 3,796                          | 3,001                            | 0 896             | 633                            | Very quiet                                    |
| 1 10- 2 10 p m   | 3,745                          | 3,139                            | 0 838             | 624                            | Very quiet                                    |
| 2 10- 3 10 p m.  | 3,707                          | 2,943                            | 0 794             | 618                            |   |

movement recorder, as well as visual observation of the animal, permits us to state that in no case was it responsible for any significant oxygen utilization after the preliminary control period (not shown) was com-

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TABLE 3

| Period  | O <sub>2</sub> absorption | CO <sub>2</sub> elimination | R Q   | O <sub>2</sub> per kgm hour | Remarks                   |
|---|---------------------------|-----------------------------|-------|-----------------------------|---------------------------|
| November 4, 1926 Dog B Wire haired terrier Weight 6,200 grams Last previous feeding November 2, 4 00 p m. |                           |                             |       |                             |                           |
|   | cc                        | cc                          |       | cc.                         |                           |
| 8 30- 9 30 a m  | 4,159                     | 2,982                       | 0 717 | 591                         | Moving occasionally       |
| 9 30-10 30 a.m.   | 3,458                     | 2,676                       | 0 774 | 495                         | Quiet                     |
| 10 32 a m   |                           |                             |       |                             | 25 grams glucose          |
| 10 45-11 15 a m   | 2,373                     | 1,872                       | 0 789 | 746                         | Fairly quiet              |
| 11 15-11 45 a m.  | 2,091                     | 1,827                       | 0 874 | 674                         | Quiet                     |
| 11 45-12 15 p m   | 1,889                     | 1,740                       | 0 921 | 610                         | Very quiet                |
| 12 15-12 45 p m   | 1,940                     | 1,715                       | 0 884 | 626                         | Very quiet                |
| 12 45- 1 45 p m   | 3,847                     | 3,063                       | 0 796 | 620                         | Quiet                     |
| 1 45- 2 45 p m  | 3,457                     | 2,679                       | 0 775 | 558                         | Movements slight          |
| 2 45- 3 45 p m  | 3 503                     | 2,554                       | 0 729 | 565                         | Quiet                     |
| November 10, 1926 Same dog Weight 5960 grams Last previous feeding November 8, a m                        |                           |                             |       |                             |                           |
|   |                           |                             |       |                             |                           |
| 8 25- 9 25 a m  | 3,276                     | 2,768                       | 0 753 | 550                         | 6 movements, then quiet   |
| 9 25-10 25 a m.   | 2,910                     | 2,267                       | 0 779 | 488                         | Fairly quiet              |
| 10 32 a m.  |                           |                             |       |                             | 25 grams dihydroxyacetone |
| 10 45-11 15 a m   | 1,485                     | 1,628                       | 1 10  | 498                         | Quiet                     |
| 11 15-11 45 a m   | 1,833                     | 1,593                       | 0 869 | 616                         | Moving                    |
| 11 45-12 15 p m.  | 1 903                     | 1 796                       | 0 944 | 638                         | Moving considerably       |
| 12 15-12 45 p m   | 1,800                     | 1,412                       | 0 784 | 604                         | Quiet                     |
| 12 45- 1 45 p m.  | 2,698                     | 2,137                       | 0 792 | 453                         | 1 slight movement         |
| 1 45- 2 45 p m  | 3,122                     | 2,312                       | 0 741 | 524                         | Moving                    |

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TABLE,  
*O<sub>2</sub> consumption, cubic centimeters per kilogram hour*

| Animal                                      | Date        | First control hour | Second control hour | First hour | Second hour | Third hour | Fourth hour     |
|---|-------------|--------------------|---------------------|------------|-------------|------------|-----------------|
| 1 Glucose tests                             |             |                    |                     |            |             |            |                 |
| A   | November 1  | 746                | 695                 | 747        | 678         | 595        |                 |
| A   | November 16 | 506                | 516                 | 494        | 520         | 542        | 454             |
| B   | November 4  | 591                | 495                 | 720        | 618         | 620        | 558             |
| B   | November 15 | 495                | 480                 | 482        | 517         | 553        | 492             |
| Average                                     |             | 584                | 546                 | 611        | 608         | 602        | 501             |
| 2 Dihydroxyacetone tests                    |             |                    |                     |            |             |            |                 |
| A   | November 3  | 760                | 679                 | 672        | 633         | 624        | 618             |
| A   | November 9  | 629                | 597                 | 653        | 689         | 583        | 603             |
| B   | November 10 | 550                | 488                 | 557        | 621         | 453        | 524             |
| B   | November 12 | 527                | 515                 | 572        | 594         | 506        | 485             |
| Average                                     |             | 616                | 570                 | 588        | 627         | 541        | 557             |
|   |             |                    |                     |            |             |            | cc per kgm hour |
| Average of 16 control periods               |             |                    |                     |            |             |            | 579             |
| Average of 15 post glucose periods          |             |                    |                     |            |             |            | 580             |
| Average of 16 post dihydroxyacetone periods |             |                    |                     |            |             |            | 578             |

hour and, therefore, not entirely suitable for this calculation, when averaged show approximately 1 per cent increased oxygen consumption over basal values. The amount of carbohydrate he calculates as being burned bears no more relation to dihydroxyacetone administration than to the glucose, and the marked variations in nitrogen excretion in the different periods ably demonstrate the essential inaccuracy of the so-called non-protein respiratory quotient in this type of

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While, as has been shown above, the total respiratory exchange is practically unchanged from the basal during the whole period of observation there are changes in oxygen consumption during the individual test periods (table 5) These, however, do not necessarily correspond with the alterations in the so-called respiratory quotient In fact, as table 6 shows, the highest  $\text{CO}_2$  output occurs in the first half-hour or hour after triose administration while the oxygen consumption (table 5) is greatest in the second hour The ratio of  $\text{CO}_2$  elimination to oxygen uptake (table 7) is consequently decidedly different from that occurring after glucose administration, in which case the rise in respiratory quotient is less abrupt and more prolonged Considering the data in tables 1 to 4 together with that of other workers, one is struck by the frequency with which the so-called respiratory quotient exceeds 1.0 Even holding the view that the respiratory quotient is an expression of dynamic equilibrium in food stuffs transformed, burned or stored, such ratios cannot be explained as due to combustion of carbohydrate alone but must include the formation of fat, and calculations of carbohydrate consumption based thereon must be in error Since, however, the oxygen intake is not decreased but the initial rise in the  $\text{CO}_2/\text{O}_2$  ratio is due to additional  $\text{CO}_2$  elimination, fat production does not appear to furnish a probable explanation for the sequence of events While it appears inherently improbable that combustion would occur in isolated stages, it may be pointed out that the change from sugar to lactic acid is anaerobic and requires no oxygen and produces no  $\text{CO}_2$  It would appear then that any additional energy expenditure is required for some other purpose and that such expenditure is accompanied by  $\text{CO}_2$  production in the absence of oxygen or that hyperventilation is the cause of the excess  $\text{CO}_2$  production, or that both these processes take place in differing proportions It is again significant that the total oxygen intake after

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- 13 Macleod, J J R , Personal communication

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Examination of the data (1, 2, 4, 5) indicates that hyperventilation has taken place and a cause for this is of interest. Increased oxygen consumption occurring later can then be explained on the basis of

TABLE 1  
*Dihydroxyacetone tolerance tests*

| Case | Time       | Blood glucose       | Blood dihydroxy acetone | Blood lactic acid   | CO <sub>2</sub> combining power |
|------|------------|---------------------|-------------------------|---------------------|---------------------------------|
|      |            | <i>mgm per cent</i> | <i>mgm per cent</i>     | <i>mgm per cent</i> | <i>volumes per cent</i>         |
| 1    | Fasting    | 85                  | 0                       | 18                  | 58*                             |
|      | 30 minutes | 90                  | 17.5                    | 50                  | 52                              |
|      | 1 hour     | 90                  | 15.8                    | 40                  | 60                              |
|      | 2 hours    | 95                  | 13.2                    | 26                  | 59                              |
|      | 3 hours    | 95                  | 8.8                     | 23                  | 62                              |
| 2    | Fasting    | 100                 | 0                       | 17                  | 64                              |
|      | 30 minutes | 120                 | 13.2                    | 24                  | 56                              |
|      | 1 hour     | 135                 | 8.8                     | 21                  | 52                              |
|      | 2 hours    | 100                 | 8.8                     | 18                  | 61                              |
|      | 3 hours    | 80                  | 4.4                     | 11                  | 63                              |
| 3    | Fasting    | 80                  | 0                       | 11                  | 67                              |
|      | 30 minutes | 110                 | 45.5                    | 31                  | 60                              |
|      | 1 hour     | 85                  | 28.0                    | 26                  | 63                              |
|      | 2 hours    | 65                  | 8.8                     | 19                  | 67                              |
|      | 3 hours    | 85                  | 4.4                     | 9                   | 67                              |
| 4    | Fasting    | 95                  | 0                       | 21                  | 64                              |
|      | 30 minutes | 80                  | 8.8                     | 38                  | 60                              |
|      | 1 hour     | 60                  | 4.4                     | 33                  | 56                              |
|      | 2 hours    | 85                  | 1.8                     | 15                  | 59                              |
|      | 3 hours    | 80                  | 0                       | 17                  | 63                              |
| 5    | Fasting    | 100                 | 0                       | 12                  | 67                              |
|      | 30 minutes | 100                 | 26.3                    | 37                  | 59                              |
|      | 1½ hours   | 75                  | 13.2                    | 31                  | 66                              |
|      | 2½ hours   | 80                  | 8.8                     | 23                  | 65                              |
| 6    | Fasting    | 85                  | 0                       | 16                  | 68                              |
|      | 30 minutes | 105                 | 17.5                    | 42                  | 58                              |

\* First blood hemolyzed

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| 1    | Fasting    | 85                  | 0                       | 18                  | 58*                             |
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| 2    | Fasting    | 100                 | 0                       | 17                  | 64                              |
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|      | 1 hour     | 85                  | 28.0                    | 26                  | 63                              |
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|------|------------|---------------------|-------------------------|---------------------|---------------------------------|
|      |            | <i>mgm per cent</i> | <i>mgm per cent</i>     | <i>mgm per cent</i> | <i>volumes per cent</i>         |
| 1    | Fasting    | 85                  | 0                       | 18                  | 58*                             |
|      | 30 minutes | 90                  | 17.5                    | 50                  | 52                              |
|      | 1 hour     | 90                  | 15.8                    | 40                  | 60                              |
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|      | 1 hour     | 135                 | 8.8                     | 21                  | 52                              |
|      | 2 hours    | 100                 | 8.8                     | 18                  | 61                              |
|      | 3 hours    | 80                  | 4.4                     | 11                  | 63                              |
| 3    | Fasting    | 80                  | 0                       | 11                  | 67                              |
|      | 30 minutes | 110                 | 45.5                    | 31                  | 60                              |
|      | 1 hour     | 85                  | 28.0                    | 26                  | 63                              |
|      | 2 hours    | 65                  | 8.8                     | 19                  | 67                              |
|      | 3 hours    | 85                  | 4.4                     | 9                   | 67                              |
| 4    | Fasting    | 95                  | 0                       | 21                  | 64                              |
|      | 30 minutes | 80                  | 8.8                     | 38                  | 60                              |
|      | 1 hour     | 60                  | 4.4                     | 33                  | 56                              |
|      | 2 hours    | 85                  | 1.8                     | 15                  | 59                              |
|      | 3 hours    | 80                  | 0                       | 17                  | 63                              |
| 5    | Fasting    | 100                 | 0                       | 12                  | 67                              |
|      | 30 minutes | 100                 | 26.3                    | 37                  | 59                              |
|      | 1½ hours   | 75                  | 13.2                    | 31                  | 66                              |
|      | 2½ hours   | 80                  | 8.8                     | 23                  | 65                              |
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|------|------------|---------------|-------------------------|-------------------|---------------------------------|
|      |            | mgm per cent  | mgm per cent            | mgm per cent      | volumes per cent                |
| 1    | Fasting    | 85            | 0                       | 18                | 58*                             |
|      | 30 minutes | 90            | 17 5                    | 50                | 52                              |
|      | 1 hour     | 90            | 15 8                    | 40                | 60                              |
|      | 2 hours    | 95            | 13 2                    | 26                | 59                              |
|      | 3 hours    | 95            | 8 8                     | 23                | 62                              |
| 2    | Fasting    | 100           | 0                       | 17                | 64                              |
|      | 30 minutes | 120           | 13 2                    | 24                | 56                              |
|      | 1 hour     | 135           | 8 8                     | 21                | 52                              |
|      | 2 hours    | 100           | 8 8                     | 18                | 61                              |
|      | 3 hours    | 80            | 4 4                     | 11                | 63                              |
| 3    | Fasting    | 80            | 0                       | 11                | 67                              |
|      | 30 minutes | 110           | 45 5                    | 31                | 60                              |
|      | 1 hour     | 85            | 28 0                    | 26                | 63                              |
|      | 2 hours    | 65            | 8 8                     | 19                | 67                              |
|      | 3 hours    | 85            | 4 4                     | 9                 | 67                              |
| 4    | Fasting    | 95            | 0                       | 21                | 64                              |
|      | 30 minutes | 80            | 8 8                     | 38                | 60                              |
|      | 1 hour     | 60            | 4 4                     | 33                | 56                              |
|      | 2 hours    | 85            | 1 8                     | 15                | 59                              |
|      | 3 hours    | 80            | 0                       | 17                | 63                              |
| 5    | Fasting    | 100           | 0                       | 12                | 67                              |
|      | 30 minutes | 100           | 26 3                    | 37                | 59                              |
|      | 1½ hours   | 75            | 13 2                    | 31                | 66                              |
|      | 2½ hours   | 80            | 8 8                     | 23                | 65                              |
| 6    | Fasting    | 85            | 0                       | 16                | 68                              |
|      | 30 minutes | 105           | 17 5                    | 42                | 58                              |

\* First blood hemolyzed.

increased work necessitated by the hyperventilation and possibly also in other ways Since it seemed apparent that hyperventilation was a



respiratory quotient to rise above 1.0 and similar claims have been made for it in diabetic treatment, it was included in the investigation along with cane sugar, which splits into glucose and fructose. Maltose, lactose, glucose and galactose, examples of aldoses, and the triatomic alcohol, glycerine, were selected for comparison with the above mentioned sugars.

TABLE 3  
*Sucrose tolerance tests*

| Case | Time       | Blood glucose | Blood fructose | Blood lactic acid | CO <sub>2</sub> combining power |
|------|------------|---------------|----------------|-------------------|---------------------------------|
|      |            | mgm. per cent | mgm. per cent  | mgm. per cent     | volumes per cent                |
| 13   | Fasting    | 105           | 0              | 17                | 63                              |
|      | 30 minutes | 150           | 15.6           | 23                | 59                              |
|      | 1 hour     | 190           | 21.0           | 25                | 54                              |
|      | 2 hours    | 145           | 15.6           | 24                | 60                              |
|      | 3 hours    | 110           | 0              | 17                | 60                              |
| 14   | Fasting    | 95            | 0              | 28                | 60                              |
|      | 30 minutes | 115           | 0              | 29                | 61                              |
|      | 1 hour     | 85            | 0              | 24                | 62                              |
|      | 2 hours    | 85            | 0              | 24                | 61                              |
|      | 3 hours    |               |                |                   | 63                              |
| 15   | Fasting    | 100           | 0              | 10                | 65                              |
|      | 30 minutes | 175           | 15.6           | 15                | 59                              |
|      | 1 hour     | 150           | 10.4           | 17                | 61                              |
|      | 2 hours    | 95            | 10.4           | 11                | 62                              |
|      | 3 hours    | 65            | 0              | 9                 | 65                              |
| 16   | Fasting    | 100           | 0              | 11                | 61                              |
|      | 30 minutes | 120           | 5.2            | 12                | 59                              |
|      | 1 hour     | 155           | 10.4           | 17                | 56                              |
|      | 2 hours    | 130           | 5.2            | 11                | 60                              |
|      | 3 hours    | 95            | 0              | 10                | 61                              |

Disturbance of the acid alkali balance is perhaps the most potent cause of hyperventilation, and for its measurement the CO<sub>2</sub> combining power (Van Slyke's precision method (6)) was employed. For certain reasons which will be discussed later the change encountered cannot be the maximal one, but it is sufficiently great to exceed many times the possible error. The origin of the change in CO<sub>2</sub> combining power which preliminary tests showed to be present was not far to

respiratory quotient to rise above 1.0 and similar claims have been made for it in diabetic treatment, it was included in the investigation along with cane sugar, which splits into glucose and fructose. Maltose, lactose, glucose and galactose, examples of aldoses, and the triatomic alcohol, glycerine, were selected for comparison with the above mentioned sugars.

TABLE 3  
*Sucrose tolerance tests*

| Case | Time       | Blood glucose | Blood fructose | Blood lactic acid | CO <sub>2</sub> combining power |
|------|------------|---------------|----------------|-------------------|---------------------------------|
|      |            | mgm. per cent | mgm. per cent  | mgm. per cent     | volumes per cent                |
| 13   | Fasting    | 105           | 0              | 17                | 63                              |
|      | 30 minutes | 150           | 15.6           | 23                | 59                              |
|      | 1 hour     | 190           | 21.0           | 25                | 54                              |
|      | 2 hours    | 145           | 15.6           | 24                | 60                              |
|      | 3 hours    | 110           | 0              | 17                | 60                              |
| 14   | Fasting    | 95            | 0              | 28                | 60                              |
|      | 30 minutes | 115           | 0              | 29                | 61                              |
|      | 1 hour     | 85            | 0              | 24                | 62                              |
|      | 2 hours    | 85            | 0              | 24                | 61                              |
|      | 3 hours    |               |                |                   | 63                              |
| 15   | Fasting    | 100           | 0              | 10                | 65                              |
|      | 30 minutes | 175           | 15.6           | 15                | 59                              |
|      | 1 hour     | 150           | 10.4           | 17                | 61                              |
|      | 2 hours    | 95            | 10.4           | 11                | 62                              |
|      | 3 hours    | 65            | 0              | 9                 | 65                              |
| 16   | Fasting    | 100           | 0              | 11                | 61                              |
|      | 30 minutes | 120           | 5.2            | 12                | 59                              |
|      | 1 hour     | 155           | 10.4           | 17                | 56                              |
|      | 2 hours    | 130           | 5.2            | 11                | 60                              |
|      | 3 hours    | 95            | 0              | 10                | 61                              |

Disturbance of the acid alkali balance is perhaps the most potent cause of hyperventilation, and for its measurement the CO<sub>2</sub> combining power (Van Slyke's precision method (6)) was employed. For certain reasons which will be discussed later the change encountered cannot be the maximal one, but it is sufficiently great to exceed many times the possible error. The origin of the change in CO<sub>2</sub> combining power which preliminary tests showed to be present was not far to

TABLE 8  
*Glycerine tolerance test*

| Case | Time       | Blood glucose       | Blood lactic acid   | CO <sub>2</sub> combining power |
|------|------------|---------------------|---------------------|---------------------------------|
|      |            | <i>mgm per cent</i> | <i>mgm per cent</i> | <i>volumes per cent</i>         |
| 31   | Fasting    | 90                  | 10                  | 57                              |
|      | 30 minutes | 95                  | 10                  | 57                              |
|      | 1 hour     | 95                  | 15                  | 61                              |
|      | 2 hours    | 95                  | 12                  | 58                              |
|      | 3 hours    | 95                  | 10                  | 58                              |
| 32   | Fasting    | 90                  | 14                  | 62                              |
|      | 30 minutes | 105                 | 14                  | 61                              |
|      | 1 hour     | 110                 | 12                  | 62                              |
|      | 2 hours    | 110                 | 12                  | 62                              |
|      | 3 hours    | 100                 | (Lost)              | 61                              |
| 33   | Fasting    | 85                  | 12                  | 67                              |
|      | 30 minutes | 80                  | 14                  | 69                              |
|      | 1 hour     | 80                  | 12                  | 70                              |
|      | 2 hours    | 80                  | 12                  | 68                              |
|      | 3 hours    | 80                  | 12                  | 68                              |

TABLE 9  
*Lactic acid tolerance test*

| Case | Time       | Blood glucose       | Blood lactic acid   | CO <sub>2</sub> combining power |
|------|------------|---------------------|---------------------|---------------------------------|
|      |            | <i>mgm per cent</i> | <i>mgm per cent</i> | <i>volumes per cent</i>         |
| 34   | Fasting    | 90                  | 11                  | 63                              |
|      | 30 minutes | 90                  | 19                  | 60                              |
|      | 1 hour     | 95                  | 19                  | 56                              |
|      | 2 hours    | 100                 | 14.5                | 61                              |
|      | 3 hours    | 95                  | 11                  | 61                              |
| 35   | Fasting    | 95                  | 11                  | 61                              |
|      | 30 minutes | 90                  | 19                  | 58                              |
|      | 1 hour     | 90                  | 17                  | 60                              |
|      | 2 hours    | 90                  | 14.5                | 60                              |
|      | 3 hours    | 90                  | 11                  | 60                              |

TABLE 8  
*Glycerine tolerance test*

| Case | Time       | Blood glucose       | Blood lactic acid   | CO <sub>2</sub> combining power |
|------|------------|---------------------|---------------------|---------------------------------|
|      |            | <i>mgm per cent</i> | <i>mgm per cent</i> | <i>volumes per cent</i>         |
| 31   | Fasting    | 90                  | 10                  | 57                              |
|      | 30 minutes | 95                  | 10                  | 57                              |
|      | 1 hour     | 95                  | 15                  | 61                              |
|      | 2 hours    | 95                  | 12                  | 58                              |
|      | 3 hours    | 95                  | 10                  | 58                              |
| 32   | Fasting    | 90                  | 14                  | 62                              |
|      | 30 minutes | 105                 | 14                  | 61                              |
|      | 1 hour     | 110                 | 12                  | 62                              |
|      | 2 hours    | 110                 | 12                  | 62                              |
|      | 3 hours    | 100                 | (Lost)              | 61                              |
| 33   | Fasting    | 85                  | 12                  | 67                              |
|      | 30 minutes | 80                  | 14                  | 69                              |
|      | 1 hour     | 80                  | 12                  | 70                              |
|      | 2 hours    | 80                  | 12                  | 68                              |
|      | 3 hours    | 80                  | 12                  | 68                              |

TABLE 9  
*Lactic acid tolerance test*

| Case | Time       | Blood glucose       | Blood lactic acid   | CO <sub>2</sub> combining power |
|------|------------|---------------------|---------------------|---------------------------------|
|      |            | <i>mgm per cent</i> | <i>mgm per cent</i> | <i>volumes per cent</i>         |
| 34   | Fasting    | 90                  | 11                  | 63                              |
|      | 30 minutes | 90                  | 19                  | 60                              |
|      | 1 hour     | 95                  | 19                  | 56                              |
|      | 2 hours    | 100                 | 14 5                | 61                              |
|      | 3 hours    | 95                  | 11                  | 61                              |
| 35   | Fasting    | 95                  | 11                  | 61                              |
|      | 30 minutes | 90                  | 19                  | 58                              |
|      | 1 hour     | 90                  | 17                  | 60                              |
|      | 2 hours    | 90                  | 14 5                | 60                              |
|      | 3 hours    | 90                  | 11                  | 60                              |

## DISCUSSION

It will be noted that the results fall into two groups, the first three sugars causing a reduction in  $\text{CO}_2$  combining power, the others not. Associated with the fall in  $\text{CO}_2$  combining power is a definite increase in the blood lactic acid, more marked in the case of dihydroxyacetone than with fructose or cane sugar as would be expected from the relative amounts of reduction of the  $\text{CO}_2$  combining power in these cases. Moreover, the return to previous values for  $\text{CO}_2$  combining power and blood lactic acid runs parallel. As in the case of the  $\text{CO}_2$  combining power alterations in the blood lactic acid after administration of the other sugars are practically negligible. In order to gain some idea of the changes involved two men were given five grams of pure lactic acid dissolved in 250 cubic centimeters of water sweetened with saccharin, and tests similar to the foregoing carried out. Table 9 shows the results obtained. In this connection it should be pointed out that lactic acid in the body is constantly being burned or reconverted to glucose or glycogen so that the values obtained for blood lactic acid as well as the resultant lowering of  $\text{CO}_2$  combining power fall short of measuring the total change taking place. Particularly will this be important in the later phases owing to the increased oxygenation consequent upon the hyperventilation. (Also since the respiratory muscles work on carbohydrate we must expect a shift of respiratory quotient toward 1.0.)

To take one method of calculating the  $\text{CO}_2$  eliminated. Palmer and Van Slyke (9) have shown that it requires 1.0 gram of  $\text{NaHCO}_3$  to raise the  $\text{CO}_2$  combining power one volume per cent in an individual weighing 38 kilograms. Taking the average depression<sup>1</sup> of the  $\text{CO}_2$  combining power at the half hour period as amounting to eight volumes per cent in an individual of 70 kilograms, 14 grams of  $\text{NaHCO}_3$  have been lost, equal to one-sixth of a formula weight or 3,750 cc of  $\text{CO}_2$  released. Providing this patient were in a basal state, 1 calorie per kilogram hour should approximate his needs, or 35 calories the requirement for the half-hour, or 7,300 cc of oxygen. With a true respiratory quotient of 0.80 (it would undoubtedly be higher on ac-

<sup>1</sup> Omitting from the average Case IV which requires one hour to attain this reduction in  $\text{CO}_2$  combining power.

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<sup>1</sup> Omitting from the average Case IV which requires one hour to attain this reduction in  $\text{CO}_2$  combining power.

absorbed in the first half hour, the formation of more lactic acid may be expected as this remaining sugar reaches the liver. It is evident from the tables that some lactic acid has disappeared at the end of an hour but a continuance of a high respiratory quotient may depend in part on incomplete re-establishment of acid alkali equilibrium, or combustion of the lactic acid, or many other factors. Should the initial  $\text{CO}_2$  released be eliminated over a longer period, as there is good reason to believe possible, there is quite sufficient to maintain high  $\text{CO}_2/\text{O}_2$  ratios for a considerable period. Attention may be called to the fact that the higher values for these ratios reported have been obtained for a very limited period and calculated on the hour basis, a procedure which examination of the protocols in the preceding paper shows is unsuitable and liable to lead to erroneous conclusions.

Turning now to another aspect of these results, we wish to call attention to the remarkable parallelism between the changes in  $\text{CO}_2$  combining power and blood lactic acid in these cases with the results of the respiratory examination in man (Mason's) or in normal dogs following the administration of dihydroxyacetone as recorded in the preceding paper. In contrast the fixation of  $\text{CO}_2$  and blood lactic acid in man and the slow rise and fall of the  $\text{CO}_2/\text{O}_2$  ratio after glucose administration to man or animals inspires confidence that such extraneous factors play little, if any, part in the alterations of the respiratory quotient after administration of the normal body sugar.

Corresponding to the decreased frequency with which the  $\text{CO}_2/\text{O}_2$  ratio exceeds 1.0, the results with fructose are somewhat less striking both in the reduction of  $\text{CO}_2$  combining power and increase in the lactic acid level (table 2). With them, however, it is still possible to calculate a  $\text{CO}_2/\text{O}_2$  ratio well above 1.0. Sucrose also shows a smaller change in the  $\text{CO}_2$  combining power and blood lactic acid (table 3). Half the administered carbohydrate was really glucose when it reached the liver and, as shown in table 4, glucose has no effect on either  $\text{CO}_2$  combining power or blood lactic acid. Likewise, maltose and lactose and galactose have no influence on these (tables 5, 6 and 7).

It would seem apparent that the extraordinary  $\text{CO}_2/\text{O}_2$  ratios reported by others (1, 2, 3, 4), as well as ourselves (5), after administration of certain carbohydrates are consequentially related to the production of lactic acid in the body and the blowing off of  $\text{CO}_2$  neces-

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way as the sugars. As table 8 shows, no lowering of  $\text{CO}_2$  combining power or rise in blood lactic acid occurs, a result which is at least consistent with this viewpoint, though by no means confirmatory of it.

Whether it be true or not that it provides the necessary chemical energy for the conversion of the ketoses to glucose, a further implication of the lactic acid production by these sugars occurs to one. For some reason lactic acid is produced when the triose or fructose is fed. The only source of lactic acid known to occur in the body is glucose or glycogen. If it could be produced from triose itself the triose administered intravenously to eviscerated animals would not remain unchanged (9). The process glycogen  $\rightarrow$  lactic acid involves an energy reduction change which must be charged against the foodstuffs initiating the lactic acid production. As, according to Meyerhof, this reduction amounts to 0.72 calorie per gram of lactic acid produced, a considerable reduction in the physiological caloric value of the foodstuff is caused directly as well as through the extra work induced by the acid stimulating respiration. In our opinion such an action does not enhance the therapeutic value of either sugar in diabetes. It is perhaps not a fortuitous circumstance that most of the important carbohydrate used by man and animals is convertible directly to glucose before absorption.

#### SUMMARY AND CONCLUSIONS

The results of the examination of the carbon dioxide combining power and blood lactic acid after the administration of certain carbohydrates have been tabulated and discussed. Certain sugars—dihydroxyacetone, fructose and cane sugar—cause a lowering of the carbon dioxide combining power and a rise in the blood lactic acid, while glucose, maltose, lactose, galactose and glycerine do not. These changes take place at the proper time to cause stimulation of respiration and the increased elimination of carbon dioxide noted when such substances are fed and explain the extraordinarily high  $\text{CO}_2/\text{O}_2$  ratios found. We would conclude that such ratios cannot be used as an index of food transformation, combustion or storage of the first substances mentioned. There appears no reason to believe that these factors interfere in the use of the ratios as respiratory quotients in the case of the other sugars examined. In view of the additional energy

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They (the cinchophen derivatives) are chemically related to salicyl and their structure indicates the presence of the quinoline ring which acts as an antipyretic. Obviously, important factors with all the compounds are general solubility and absorbability. The poor solubility and absorbability probably explain the innocuousness of neocinchophen. Finally, the combined use of morphine and quinine, both of which are chemically different from all the drugs thus far mentioned but which are nevertheless therapeutically efficient in rheumatic fever, indicates the relative unimportance of chemical composition and structure of these therapeutic drugs and of the specificity of salicyl in this disease. The speculations on the chemical side of the question have not led to anything definite pertaining to the mechanism of anti-rheumatic action.

Since this review Masters (5) has shown that sodium salicylate has no effect on the normal human electrocardiogram and therefore does not account for any of the electrocardiographic changes noted in rheumatic fever. Furthermore, Levy and Turner (6) have shown that following salicylate therapy, in addition to the usual anti-symptomatic effect, there was a gradual reduction of the P-R interval to within normal limits in patients with rheumatic heart disease. On withdrawing the drug a prolongation of the conduction time recurred. We know of no such studies with tolysin.

Because we had under observation carefully controlled cases of juvenile rheumatic fever with no arthritis but with an active infection evidenced by fever, loss of weight and leucocytosis, we were interested in observing the action of tolysin on this phase of the disease.

#### METHODS

In selecting the cases it was necessary to know that an active infection was present and demonstrable, and careful allowance was made for the natural course of the disease. It is well known that the acute forms may subside more or less completely regardless of treatment although subject to recurrences over a period of years. Chronic rheumatic carditis manifests too few signs of infection to be good material for study. We have, therefore, selected six carefully controlled cases from the Children's Heart Hospital of Philadelphia all of the subacute type. In these, three well-recognized criteria of infection were present, *viz* fever, leucocytosis and loss of weight, all of which had been stationary for several months previous to treatment. It is to be noted that during treatment none of these cases had arthritis or chorea, but that all had definite active cardiac lesions.

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The administration of the drug was oral and the dosage is shown in the table. This has exceeded in our children the efficient therapeutic dose recognized for adults by Hanzlık (1).

#### TREATMENT AND RESULTS

Six children with rheumatic heart disease were treated with tolysin and the results are shown in table 1. The diagnosis in all these cases was rheumatic heart disease (active) with mitral stenosis and insufficiency, and enlargement of the heart. There were no arrhythmias and although the lesions were fairly severe, none of these patients showed failure of compensation. The pulse rate was not affected by treatment in any of these patients.

The absence of any demonstrable effect of tolysin upon the weight, temperature and leucocytosis in this type of rheumatic heart disease is evident from the above data.

#### *Toxicity*

Toxic symptoms of the drug were not found, although sought for in every case. Two children each vomited once during the course of treatment but as they were not sick before or after the vomited dose, and as the trouble was very obviously due to the mechanical difficulty of children swallowing pills, the form of administration and not the action of the drug was blamed for this. None of the cases showed tinnitus aurium, or other toxic effects and from clinical observations we agree with Barbour and Lozinsky (7) that tolysin is non-toxic.

#### *Comment*

It is evident that such cases are a very severe test of any drug therapy. The low grade fever of chronic tuberculosis would perhaps be a comparable condition.

The failure of tolysin to act on this condition is presumably due to the fact that these patients with very low temperatures are not suitable subjects for its antipyretic effects. Hanzlık (1) makes it quite clear that whatever action these drugs may have on arthritis or carditis, the results are almost entirely accounted for by antipyresis and analgesia. In Miller and Boots (3) cardiac series where the fever was

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condition of the kidneys in cardiac patients after having returned to a state of compensation and in doing so have correlated the tests which are most frequently used

In patients recently recovered from attacks of heart failure, tests were made a few days before sitting up. The patients were taking ward diet, free of salt except that used in cooking. The tests selected were (1) the urea concentration index (the Van Slyke index) described by Van Slyke, Linder, Hiller, Leiter and McIntosh (1926), (2) the phenolsulphonaphthalein test, (3) the concentration test, and (4) the dilution or water test

1 The significance of ascertaining the concentrating power of the kidneys for urea under standard conditions is stated by McIntosh and Reimann (1926) to be "The significance of the urea concentration index may be described by stating that it represents the number of times the kidneys concentrate urea in excreting it from the blood into the urine, when the urine volume output is at the average normal rate of 1 cc per minute or 1 cc per hour per kilo body weight." The index may also be regarded as representing the number of cubic centimeters of blood cleared of urea by the kidneys when urine is being excreted at the rate of 1 cubic centimeter per minute. Values of 35 to 80 for the index are regarded as normal.

2 Phenolsulphonaphthalein 1 cc was injected intravenously. Urine specimens were collected at the end of 1 and of 2 hours. The amount of the dye excreted was then estimated. The dye was given at the end of the urea concentration test. Excretion of 55 per cent or more of the dye in 2 hours was considered to be normal.

3 The aim of the concentration test is to study the behavior of the kidneys under mild stress. In 1914 Hedinger and Schlayer (1914) introduced a test diet for cases of nephritis which was further elaborated by Mosenthal (1915) in 1915. The test as we have used it was devised in this hospital by Lundsgaard. The patients are given 3 dry meals. Each meal consists of bread (toasted) 65 grams, butter 15 grams, eggs (scrambled) 100 grams, cream cheese 25 grams, and jam or jelly 15 grams to 20 grams. The caloric value of this meal is 600 calories, a total of 1800 calories. No water is given from midnight of the day preceding the test until its end. On the morning of the test the patient voids at 6 a.m. This specimen is discarded. He voids again at 7 a.m., this specimen being saved. The dry meals are given at 7:30, 10:00 and 11:40 a.m. The patient voids at 9 and at 11 a.m., at 1 and at 3 p.m., each specimen is saved separately. The test ends after the specimen is collected at 3 p.m. The amount and specific gravity of each specimen are estimated. In normal individuals the specific gravity rises to 1.030 during this test. We have however arbitrarily decided to regard 1.025 to 1.030 as within the normal limits for the purposes of this study.

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TABLE 1  
*Summary of data on compensated cardiac patients*

| Case number<br>Sex† | Hospital number | Age | Cardiac diagnosis* |  |                | Blood pressure       | Attacks of heart failure |                   |        | Type of failure             | Renal function                 |               |            |                           |                     | Subsequent history |                        |
|---------------------|-----------------|-----|--------------------|--|----------------|----------------------|--------------------------|-------------------|--------|-----------------------------|--------------------------------|---------------|------------|---------------------------|---------------------|--------------------|------------------------|
|                     |                 |     | Etiological        | Anatomical   | Physio-logical |                      | First<br>years ago       | Last<br>years ago | Number |                             | Concentration test,<br>gravity | Dilution test | Urea index | Phenolphthalein excretion | Blood urea nitrogen | Condition          | Years after last tests |
| 1 (M)               | 5269            | 54  | Hypertension       | Slight enlargement of heart  | N.R.           | 164<br>98 → 80       | 0                        | 0                 | 0      | Palpitation                 | 1 025                          | 705 1 005     | 30 0       | 88 3 0                    | 181                 | Well               | 3½                     |
| 2 (1) (M)           | 4631            | 50  | Hypertension       | Cardiac hypertrophy dilatation of aorta V.P.L.                       | N.R., V.P.C.   | 228<br>115           | 0                        | 0                 | 0      | Fatigue                     |                                |               | 44 0       | 68 0 0                    | 176                 |                    |                        |
| (2)                 | 4842            | 51  | Hypertension       | Cardiac hypertrophy dilatation of aorta, V.P.L.                      | N.R., V.P.C.   | 210<br>120           | 0                        | 0                 | 0      | Fatigue                     |                                |               | 51 0       | 0                         | 151                 | Well               | 4½                     |
| 3 (M)               | 4823            | 66  | Arteriosclerosis   | Cardiac hypertrophy mitral insufficiency V.P.L.                      | A.F.           | 140<br>80 → 60       | Pres ent                 | Pres ent          | 1      | Edema pulmonary congestion  |                                |               | 54 2       | 0                         | 177                 | Died§              | During the admission   |
| 4 (M)               | 5001            | 72  | Arteriosclerosis   | Cardiac hypertrophy mitral insufficiency chronic myocarditis, V.P.L. | A.F.           | 100-120<br>60-90     | 4                        | Pres ent          | 2      | Edema, ascites, hydrothorax | 1 024                          | 851 1 005     | 59 0       | 61 9 0                    | 179                 | Well               | 4½                     |
| 5 (1) (F)           | 4941            | 53  | Hypertension       | V.P.L.   | N.R.           | 160 → 120<br>85 → 65 | 0                        | 0                 | 0      | Fatigue                     | 1 025                          | 615 1 006     | 66 0       | 76 0 0                    | 127                 |                    |                        |
| (2)                 | 4996            | 53  | Hypertension       | V.P.L.   | N.R.           | 110-130<br>65-82     | 0                        | 0                 | 0      | Fatigue                     | 1 028                          | 733 1 007     | 120 0      | 78 4 0                    | 172                 |                    |                        |

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|                     |                 |     | Etiological        | Anatomical   | Physio-logical |                       | First<br>years<br>ago    | Last<br>years<br>ago | Number |                             | Concentration test,<br>highest specific gravity | Amount<br>cc | Lowest specific gravity | Dilution test | Urea index | Phenolsulphone<br>phthalate excretion<br>per cent | mg<br>per<br>liter | Condition | Years after last tests |
| 1 (M)               | 5269            | 54  | Hypertension       | Slight enlargement of heart  | N.R.           | 164<br>98 → 140<br>80 | 0                        | 0                    | 0      | Palpitation                 | 1 025   | 705          | 1 005                   |               | 30 0       | 88 3 0  | 181                | Well      | 3½                     |
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| (2)                 | 4996            | 53  | Hypertension       | V.P.L.   | N.R.           | 110-130<br>65-82      | 0                        | 0                    | 0      | Fatigue                     | 1 028   | 733          | 1 007                   |               | 120 0      | 78 4 0  | 172                |           |                        |

TABLE 1—Continued

| Case number<br>Sex† | Hospital number | Age    | Cardiac diagnosis*                                   |   |                    | Blood pressure    | Attacks of heart failure |          |        | Type of failure  | Renal function                                 |                         |                         |            |                                    | Subsequent history  |           |                        |
|---------------------|-----------------|--------|--|---|--------------------|-------------------|--------------------------|----------|--------|------------------|--|-------------------------|-------------------------|------------|------------------------------------|---------------------|-----------|------------------------|
|                     |                 |        | Etiological  | Anatomical  | Physio-logical     |                   | First                    | Last     | Number |                  | Concentration test<br>Highest specific gravity | Dilution test<br>Amount | Lowest specific gravity | Urea index | Phenolsulphone-phthalein excretion | Blood urea nitrogen | Condition | Years after last tests |
| 13 (1)<br>(M)       | 6323            | 51 yrs | Hypertension   | Slight cardiac hypertrophy  | N R.               | 200<br>130<br>130 | 0                        | 0        | 0      | Pain of the eyes | 1 025  | 1,465                   | 1 001                   | 47 8       | 57 1                               | 0 099               |           |                        |
| (2)                 | 6392            | 51     | Hypertension   | Slight cardiac hypertrophy  | N R.               | 185<br>140        | 0                        | 0        | 0      | Pain of the eyes | 1 026  | 1 305                   | 1 005                   | 64 0       | 62 8                               | 0 103               | Well      | 3                      |
| 14<br>(M)           | 5225            | 65     | Arteriosclerosis                                     | Cardiac hypertrophy chronic myocarditis mitral insufficiency, aortic roughening, V.P R. | N R.               | 150 130<br>110 80 | Pres-ent                 | Pres-ent | 1      | Edema            | 1 028  | 720                     | 1 005                   | 70 3       | 56 3                               | 0 206               | Died      | 3                      |
| 15<br>(M)           | 5285            | 20     | Rheumatism?  | Cardiac hypertrophy cardiac dilatation, mitral stenosis, mitral insufficiency, V P R.   | N R., s L.         | 100<br>60         | Pres-ent                 | Pres-ent | 1      | Dyspnea          | 1 035  | 997                     | 1 001                   | 52 3       | 67 6                               | 0 138               | Died      | 3½                     |
| 16<br>(M)           | 6183            | 56     | Arteriosclerosis                                     | Cardiac hypertrophy, coronary thrombosis  | N R., hypertension | 170<br>110        | 1                        | 1        | 1      | Pain             | 1 028  | 183                     | 1 018                   | 30 7       | 71 8                               | 0 087               | Well      | 3                      |
| 17 (1)<br>(M)       | 5265            | 18     | Acute rheumatic fever at 9 years tonsillitis, chorea | Chronic myocarditis, V P R.   | N R<br>A.P C       | 110<br>65         | Pres-ent                 | Pres-ent | 1      | Pain A P C       | 1 029  | 830                     | 1 006                   | 106 0      | 107 4                              | 0 071               |           |                        |
| (2)                 | 5645            | 19     | Acute rheumatic fever at 9 years tonsillitis, chorea | Chronic myocarditis, V P R.   | N.R.<br>A.P C      | 105<br>65         | 1                        | Pres-ent | 2      | Pain, A P C      | 1 037  | 885                     | 1 001                   | 67 4       | 84 3                               | 0 157               | Well      | 2                      |

TABLE 1—Continued

| Case number<br>Sex† | Hospital number | Age | Cardiac diagnosis*                                   |   | Blood pressure     | Attacks of heart failure |          |          | Type of failure | Renal function   |  |               |                         |            | Subsequent history                 |                     |           |                        |
|---------------------|-----------------|-----|--|---|--------------------|--------------------------|----------|----------|-----------------|------------------|--|---------------|-------------------------|------------|------------------------------------|---------------------|-----------|------------------------|
|                     |                 |     | Etiological  | Anatomical  |                    | Physio-logical           | First    | Last     |                 | Number           | Concentration test<br>Highest specific gravity | Dilution test |                         | Urea index | Phenolsulphone-phthalein excretion | Blood urea nitrogen | Condition | Years after last tests |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  | Amount        | Lowest specific gravity |            |                                    |                     |           |                        |
| 13<br>(1)<br>(M)    | 6323            | 51  | Hypertension   | Slight cardiac hypertrophy  | N R.               | 200<br>130<br>185<br>140 | 0        | 0        | 0               | Pain of the eyes | 1 025  | 1,465         | 1 001                   | 47 8       | 57 1 0                             | 099                 |           |                        |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |
| 14<br>(2)<br>(M)    | 6392            | 51  | Hypertension   | Slight cardiac hypertrophy  | N R.               | 185<br>140               | 0        | 0        | 0               | Pain of the eyes | 1 026  | 1 305         | 1 005                   | 64 0       | 62 8 0                             | 103                 | Well      | 3                      |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |
| 15<br>(M)           | 5225            | 65  | Arteriosclerosis                                     | Cardiac hypertrophy chronic myocarditis mitral insufficiency, aortic roughening, V.P.R. | N R.               | 150<br>110<br>130<br>80  | Pres-ent | Pres-ent | 1               | Edema            | 1 028  | 720           | 1 005                   | 70 3       | 56 3 0                             | 206                 | Died      | 2                      |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |
| 16<br>(M)           | 5285            | 20  | Rheumatism?  | Cardiac hypertrophy cardiac dilatation, mitral stenosis, mitral insufficiency, V.P.R.   | N R., S L.         | 100<br>60                | Pres-ent | Pres-ent | 1               | Dyspnea          | 1 035  | 997           | 1 001                   | 52 3       | 67 6 0                             | 138                 | Died      | 3†                     |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |
| 17<br>(1)<br>(M)    | 6183            | 56  | Arteriosclerosis                                     | Cardiac hypertrophy, coronary thrombosis  | N R., hypertension | 170<br>110               | †        | †        | 1               | Pain             | 1 028  | 183           | 1 018                   | 30 7       | 71 8 0                             | 087                 | Well      | 3                      |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |
| 18<br>(2)<br>(M)    | 5265            | 18  | Acute rheumatic fever at 9 years tonsillitis, chorea | Chronic myocarditis, V.P.R.   | N R. A.P.C         | 110<br>65                | Pres-ent | Pres-ent | 1               | Pain A.P.C       | 1 029  | 830           | 1 006                   | 106 0      | 107 4 0                            | 071                 |           |                        |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |
| 19<br>(2)<br>(M)    | 5645            | 19  | Acute rheumatic fever at 9 years tonsillitis, chorea | Chronic myocarditis, V.P.R.   | N R. A.P.C         | 105<br>65                | 1        | Pres-ent | 2               | Pain, A.P.C      | 1 037  | 885           | 1 001                   | 67 4       | 84 3 0                             | 157                 | Well      | 2                      |
|                     |                 |     |  |   |                    |                          |          |          |                 |                  |  |               |                         |            |                                    |                     |           |                        |



TABLE 1—Concluded

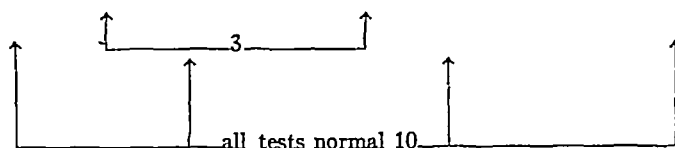
| Case number<br>Sex† | Hospital number | Age       | Cardiac diagnosis* |  |                | Blood pressure        | Attacks of heart failure |                      |        | Type of failure   | Renal function                                 |              |                         |               |            | Subsequent history                                |   |
|---------------------|-----------------|-----------|--------------------|--|----------------|-----------------------|--------------------------|----------------------|--------|---|--|--------------|-------------------------|---------------|------------|---|---|
|                     |                 |           | Etiological        | Anatomical   | Physio-logical |                       | First<br>years<br>ago    | Last<br>years<br>ago | Number |   | Concentration test<br>Highest specific gravity | Amount<br>cc | Lowest specific gravity | Dilution test | Urea index | Phenolsulphone<br>phthalein excretion<br>per cent | Blood urea nitrogen<br>gms per<br>liter |
| 24<br>(M)           | 5584            | 54<br>yrs | Arteriosclerosis   | Cardiac hypertrophy<br>chronic myocarditis mi<br>tral insufficiency aortic<br>roughening, V P L. | N R<br>V P C   | 100<br>80             | 1<br>4                   | Pres-<br>ent         | 1      | Edema ascites<br>hydrothorax  | 1 030  | 94 1         | 021                     | 34 1          | 64 40 322  | Not<br>known                                      |   |
| 25<br>(M)           | 5204            | 30        | Unknown            | Chronic myocarditis, mitral<br>insufficiency   | N R.           | 100<br>70             | Pres-<br>ent             | Pres-<br>ent         | 1      | Dyspnea   | 1 034  | 899 1        | 004                     | 90 2          | 87 50 136  | Well  | 3½                                      |
| 26<br>(M)           | 5829            | 26        | Hypertension       | Mitral insufficiency   | N R            | 160<br>80 → 130<br>65 | Pres-<br>ent             | Pres-<br>ent         | 1      | Pain  | 1 026  | 640 1        | 003                     | 59 8          | 70 70 130  | Well  | 1½                                      |
| 27<br>(M)           | 5424            | 52        | Unknown            | Cardiac hypertrophy<br>chronic myocarditis, mi<br>tral insufficiency, V P L.                     | N R            | 125<br>90             | Pres-<br>ent             | Pres-<br>ent         | 1      | Edema hydro-<br>thorax  | 1 025  | 830 1        | 001                     | 48 5          | 67 40 142  | Died  | 1½                                      |
| 28<br>(M)           | 5401            | 27        | Rheumatism?        | Cardiac hypertrophy mitral<br>stenosis mitral insuffi-<br>ciency V P R                           | A F            | 100<br>65             | 6                        | Pres-<br>ent         | 5      | Edema pulmo-<br>nary conges-<br>tion, pulmo-<br>nary hemor-<br>rhages | 1 031  | 395 1        | 003                     | 54 2          | 93 50 189  | Died§   | 1½                                      |
| 29<br>(F)           | 6163            | 61        | Arteriosclerosis   | Cardiac hypertrophy<br>chronic myocarditis mi<br>tral insufficiency                              | A F<br>V P C   | 135<br>85             | 1½                       | Pres-<br>ent         | 1      | Edema   | 1 017  | 385 1        | 005                     | 42 7          | 53 30 210  | Well  | 1½                                      |

TABLE 1—Continued

| Case number<br>Sex† | Hospital number | Age | Cardiac diagnosis* |   |                | Blood pressure        | Attacks of heart failure |              |        | Type of failure   | Renal function                                 |  |                 |   |           | Blood urea nitrogen | Subsequent history     |  |
|---------------------|-----------------|-----|--------------------|---|----------------|-----------------------|--------------------------|--------------|--------|---|--|--|-----------------|---|-----------|---------------------|------------------------|--|
|                     |                 |     | Etiological        | Anatomical  | Physio-logical |                       | First                    | Last         | Number |   | Concentration test<br>Highest specific gravity | Dilution test<br>Amount<br>Lowest specific gravity | Urea index      | Phenolsulphone<br>phthalein excretion<br>per cent<br>filter | Condition |                     | Years after last tests |  |
| 24<br>(M)           | 5584            | 54  | Arteriosclerosis   | Cardiac hypertrophy<br>chronic myocarditis<br>mitral insufficiency aortic<br>roughening, V P L. | N R<br>V P C   | 100<br>80             | 1<br>years<br>ago        | Pres-<br>ent | 1      | Edema ascites<br>hydrothorax  | 1 030  | 94 1 021   | 34 1 64 4 0 322 | Not known   |           |                     |                        |  |
| 25<br>(M)           | 5204            | 30  | Unknown            | Chronic myocarditis, mitral<br>insufficiency  | N R.           | 100<br>70             | Pres<br>ent              | Pres-<br>ent | 1      | Dyspnea   | 1 034  | 899 1 004  | 90 2 87 5 0 136 | Well  |           | 3½                  |                        |  |
| 26<br>(M)           | 5829            | 26  | Hypertension       | Mitral insufficiency  | N R            | 160<br>80 → 130<br>65 | Pres-<br>ent             | Pres-<br>ent | 1      | Pain  | 1 026  | 640 1 003  | 59 8 70 7 0 130 | Well  |           | 1½                  |                        |  |
| 27<br>(M)           | 5424            | 52  | Unknown            | Cardiac hypertrophy<br>chronic myocarditis, mi<br>tral insufficiency, V P L                     | N R            | 125<br>90             | Pres<br>ent              | Pres<br>ent  | 1      | Edema hydro-<br>thorax  | 1 025  | 830 1 001  | 48 5 67 4 0 142 | Died  |           | 1½                  |                        |  |
| 28<br>(M)           | 5401            | 27  | Rheumatism?        | Cardiac hypertrophy mitral<br>stenosis mitral insuffi-<br>ciency V P R                          | A F            | 100<br>65             | 6<br>Pres-<br>ent        | Pres-<br>ent | 5      | Edema pulmo-<br>nary congest-<br>ion, pulmo-<br>nary hemor-<br>rhages | 1 031  | 395 1 003  | 54 2 93 5 0 189 | Died§   |           | 1½                  |                        |  |
| 29<br>(F)           | 6163            | 61  | Arteriosclerosis   | Cardiac hypertrophy<br>chronic myocarditis mi<br>tral insufficiency                             | A. I.<br>V P C | 135<br>85             | 1½<br>Pres-<br>ent       | Pres-<br>ent | 1      | Edema   | 1 017  | 385 1 005  | 42 7 53 3 0 210 | Well  |           | 7½                  |                        |  |

TABLE 2  
*A summary of results of tests of renal function in cardiac patients*

| Van Slyke index |        | Concentration test |        |         | Dilution test |        |         | Phenolsulphonethalein test |        |         |
|-----------------|--------|--------------------|--------|---------|---------------|--------|---------|----------------------------|--------|---------|
| Low             | Normal | Low                | Normal | No data | Low           | Normal | No data | Low                        | Normal | No data |
| 7               | 28     | 9                  | 22     | 4       | 13            | 18     | 4       | 1                          | 33     | 1       |



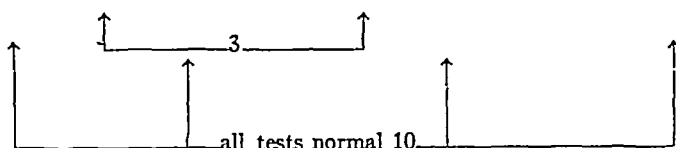
phenolsulphonethalein was normal in all except one (case 10) of 35 patients. The Van Slyke index was normal in 28 patients (41 tests) (tables 1 and 2), and below normal, though in no instance greatly so, in 7 patients (9 tests). In 10 patients the kidneys failed to concentrate urine to a specific gravity of 1.026 to 1.030, though in only one case did it fall below a specific gravity of 1.020 (case 29, 1.017). In 17 patients the results first obtained by use of the dilution test were abnormal. In 7 the only abnormality was failure to excrete 750 cc or more of the 1000 cc of water ingested. In 3, although the specific gravity did not fall to 1.005, a normal amount of water was nevertheless excreted. In the other 8 patients<sup>1</sup> (that is to say of the 17) the amount excreted was less than 750 cc and beside the specific gravity did not fall to 1.005. Five of the 17 showed abnormalities in the concentration test as well. In one patient (case 34) after prolonged rest in bed, when the blood pressure fell, there were decreased values except in the concentration and phenolsulphonethalein tests. After taking a salt free diet for 6 weeks when the blood pressure fell further, the renal function improved, as indicated by the presence of normal dilution although concentration rose only to 1.022. In this patient, the diagnosis is not certain. He may have passed through a stage of acute nephritis to which hypertension was secondary and not primary or essential. In 10 of the 35 patients the values at one time were normal in all the tests, while in 25 the function was decreased at some time in one or more of the tests.

<sup>1</sup> Several patients during several years fall now in one group and now in another due to change in the renal function even according to the same tests.

TABLE 2

*A summary of results of tests of renal function in cardiac patients*

| Van Slyke index |        | Concentration test |        |         | Dilution test |        |         | Phenolsulphonaphthalein test |        |         |
|-----------------|--------|--------------------|--------|---------|---------------|--------|---------|------------------------------|--------|---------|
| Low             | Normal | Low                | Normal | No data | Low           | Normal | No data | Low                          | Normal | No data |
| 7               | 28     | 9                  | 22     | 4       | 13            | 18     | 4       | 1                            | 33     | 1       |

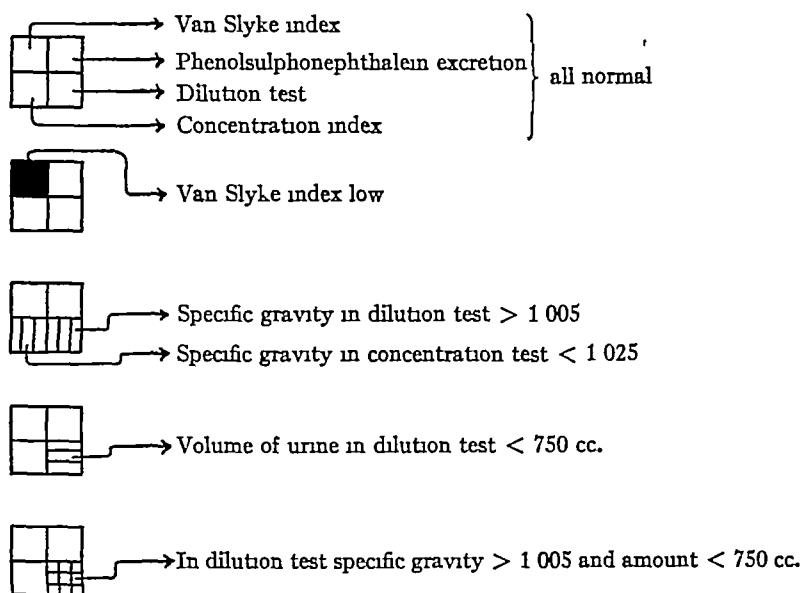


phenolsulphonaphthalein was normal in all except one (case 10) of 35 patients. The Van Slyke index was normal in 28 patients (41 tests) (tables 1 and 2), and below normal, though in no instance greatly so, in 7 patients (9 tests). In 10 patients the kidneys failed to concentrate urine to a specific gravity of 1.026 to 1.030, though in only one case did it fall below a specific gravity of 1.020 (case 29, 1.017). In 17 patients the results first obtained by use of the dilution test were abnormal. In 7 the only abnormality was failure to excrete 750 cc or more of the 1000 cc of water ingested. In 3, although the specific gravity did not fall to 1.005, a normal amount of water was nevertheless excreted. In the other 8 patients<sup>1</sup> (that is to say of the 17) the amount excreted was less than 750 cc and beside the specific gravity did not fall to 1.005. Five of the 17 showed abnormalities in the concentration test as well. In one patient (case 34) after prolonged rest in bed, when the blood pressure fell, there were decreased values except in the concentration and phenolsulphonaphthalein tests. After taking a salt free diet for 6 weeks when the blood pressure fell further, the renal function improved, as indicated by the presence of normal dilution although concentration rose only to 1.022. In this patient, the diagnosis is not certain. He may have passed through a stage of acute nephritis to which hypertension was secondary and not primary or essential. In 10 of the 35 patients the values at one time were normal in all the tests, while in 25 the function was decreased at some time in one or more of the tests.

<sup>1</sup> Several patients during several years fall now in one group and now in another due to change in the renal function even according to the same tests.

dominated. In the fourth group are 3 patients (cases 2, 5 and 9) in whom heart failure manifested itself as *fatigue*. In the fifth group is one patient (case 1) who complained only of *palpitation*. No special

FIG 1 In this figure the renal functions of patients are charted at the age which they were estimated. Each column represents a patient. The ordinates represent years of age. Symbols indicate renal function, and the etiology of the cardiac disease. The years in which infections occurred, cardiac lesions were diagnosed, symptoms first appeared and attacks of heart failure occurred are also indicated.

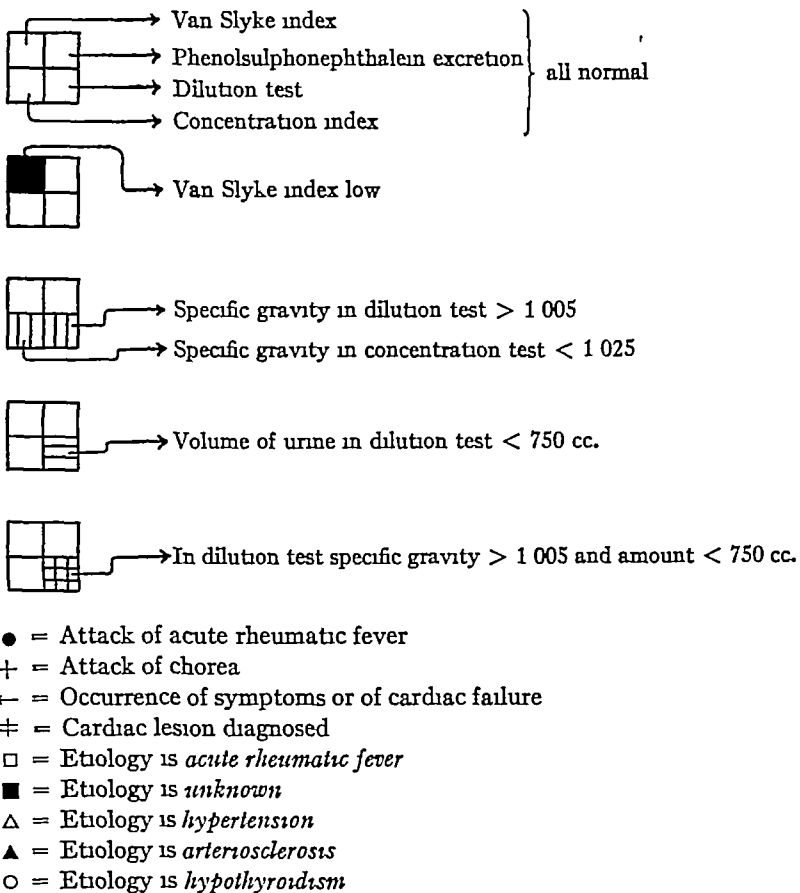


- = Attack of acute rheumatic fever
- + = Attack of chorea
- ← = Occurrence of symptoms or of cardiac failure
- ≠ = Cardiac lesion diagnosed
- = Etiology is *acute rheumatic fever*
- = Etiology is *unknown*
- △ = Etiology is *hypertension*
- ▲ = Etiology is *arteriosclerosis*
- = Etiology is *hypothyroidism*

complaints were to be elicited from 2 patients (cases 13 and 34) who were the subjects of hypertension. Many of the impairments in renal function were discovered in the patients subject to attacks of *con-*

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complaints were to be elicited from 2 patients (cases 13 and 34) who were the subjects of hypertension. Many of the impairments in renal function were discovered in the patients subject to attacks of *con-*

years to one month in 35 patients. Impairment of function did not appear to vary with the duration of the disease, whether months or years. Impairments occurred about as frequently in those who had had only one, as in those who had had repeated attacks. The degree of impairment in short did not parallel the number of attacks of heart failure (see discussion). Nor did there appear to be an outspoken relation between the duration of heart disease<sup>3</sup> and the degree of impairment, so far as the concentrating and diluting functions of the kidneys are concerned.

*Correlation of age and renal function in patients with heart disease*

There are 50 observations in 38 patients (Figure 1). Twelve (cases 8, 12, 15, 17, 19, 22, 25, 26, 28, 31, 34, and 35) range in age between 15 and 30 years. In seven (cases 8, 12, 15, 17, 19, 28 and 31) of these, or about 60 per cent, the function appeared normal in all the tests. But in 23 patients ranging in age between 38 and 72 years, this was true in 3 only (cases 5, 13 and 27). Although the number of cases is too few for statistical statement, impairments in renal function are certainly more frequent in heart patients in the decades after 30 years.

*Blood urea in heart disease* The blood urea was below 0.200 gram per liter in all except 3 patients.

#### DISCUSSION

We have found, on the whole, little impairment in those renal functions which we have been able to measure in patients suffering from chronic heart disease. The number studied is of course small for statistical treatment. The Van Slyke index was abnormal in only 8 patients and phenolsulphonephthalein excretion was diminished in only one. The most frequent impairment was the diluting ability of the kidneys, the concentrating function was second. This was the situation during the stage of compensation. Little or no permanent damage to the kidneys need become established for many years. During the stage of congestion renal function as measured by the Van Slyke index, the phenolsulphonephthalein excretion, and the Mosenthal test diet, is however greatly diminished. Afterwards some impairment becomes evident.

<sup>3</sup> The duration of heart disease dates from the time when a diagnosis of heart disease was made, it need not of course coincide with the date of the first attack of heart failure.

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sis and insufficiency of rheumatic origin. In the *first* (case 12) all the tests for renal function were normal after recovery from a third attack of heart failure. One year later, after recovery from a fourth attack, he was no longer able to excrete urine of low specific gravity. The amount also decreased as was seen in the dilution test. After the eighth attack two years later, both functions, concentrating as well as diluting, were abnormal. While damage to the heart was progressing continuously change in kidney function also occurred. The general condition and the behavior of the kidneys took a parallel downward course. The *second* patient (case 19) likewise exhibited normal renal functions after recovery from a first attack of heart failure. Three years later, after the third attack, he could no longer excrete the normal amount of water in the dilution test, nor could he lower the specific gravity to 1.005. His capacity for exertion had meanwhile diminished. The *third* patient (case 22) had suffered from heart disease for 14 years and had suffered from 6 attacks of heart failure when the first observations were made. These revealed abnormality in the concentration test. One year later, after the seventh attack, the dilution as well as the concentration test was abnormal. During this time he failed rapidly.

Three patients (cases 5, 17, and 23, fig. 1) showed progressive improvement in renal function over a period of several years, clinical improvement occurred at the same time. A fourth patient (case 6) remained unchanged over a period of 5 years, both from the point of view of the clinical course and of the kidneys.

Our observations as we have said, include however neither a sufficiently large number of patients nor do they cover sufficiently long periods to warrant our drawing conclusions on the meaning of the tests we have used from the point of view of prognosis. The situation is in fact confusing. Some patients are alive and are carrying on work without signs of heart failure, though their renal functions are as greatly diminished as were those in others shortly before death.

Deterioration in the renal functions was most common in the arteriosclerotic and hypertensive groups in which they were normal in only two individuals (cases 5 and 13), less common in the acute rheumatic group in which were most of the patients with normal function. Beyond the age of 30 normal function was present in only three (cases 5, 13 and 27). The lower age may be 40 or 50 years if larger numbers

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4 In 17 patients, that is to say in one half the patients studied, the dilution test revealed abnormality either in the ability to excrete the normal amount of water or in the failure of the specific gravity to fall or in both

5 The concentration test showed impairment in 10 patients

6 Diminished renal function was found in all except 3 patients who were more than 30 years of age

7 A correlation exists between arterio-sclerosis and hypertension and decrease in renal function

8 The impairments of renal function were found more frequently in patients who suffered from congestive heart failure

9 There was no correlation between duration of heart disease and impairment in renal function

#### CONCLUSIONS

Although the number of patients is too small to make statistical inferences, the following facts emerge from analysis of the data

1 After 30 years of age, normal renal function is found rarely in patients with cardiac disease

2 Normal function is rare in patients with circulatory disease of arterio-sclerotic or hypertensive etiology

2a Conclusions 1 and 2 are correlated, since arterio-sclerosis and hypertension are diseases of the later decades

3 Impairments of renal function were found most frequently in patients subject to repeated attacks of congestive heart failure

4 Although correct in general, conclusion 3 requires modification by the statement that the degree of impairment did not parallel the number of attacks of failure

4a During intervals between attacks of heart failure there may be no impairment of renal function

5 There was no correlation between the duration of heart disease and the degree of impairment

5a There was no correlation between the length of time since the onset of the first attack of heart failure and the degree of impairment

6a The Van Slyke index of urea excretion and the phenolsulphone-phthalein excretion are usually normal

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6 Diminished renal function was found in all except 3 patients who were more than 30 years of age

7 A correlation exists between arterio-sclerosis and hypertension and decrease in renal function

8 The impairments of renal function were found more frequently in patients who suffered from congestive heart failure

9 There was no correlation between duration of heart disease and impairment in renal function

#### CONCLUSIONS

Although the number of patients is too small to make statistical inferences, the following facts emerge from analysis of the data

1 After 30 years of age, normal renal function is found rarely in patients with cardiac disease

2 Normal function is rare in patients with circulatory disease of arterio-sclerotic or hypertensive etiology

2a Conclusions 1 and 2 are correlated, since arterio-sclerosis and hypertension are diseases of the later decades

3 Impairments of renal function were found most frequently in patients subject to repeated attacks of congestive heart failure

4 Although correct in general, conclusion 3 requires modification by the statement that the degree of impairment did not parallel the number of attacks of failure

4a During intervals between attacks of heart failure there may be no impairment of renal function

5 There was no correlation between the duration of heart disease and the degree of impairment

5a There was no correlation between the length of time since the onset of the first attack of heart failure and the degree of impairment

6a The Van Slyke index of urea excretion and the phenolsulphone-phthalein excretion are usually normal

*Case 20* The anatomical diagnosis was calcification of the aortic valves, stenosis of the aortic valves, cardiac hypertrophy, advanced atherosclerosis of the aorta, moderate atheromatosis of the aortic cusp of the mitral valve and of the coronary vessels, arteriosclerosis of the kidneys, infarcts of the kidneys, cyanotic induration of the liver, passive congestion of the spleen and kidneys, ascites, edema of the legs and intestines, serous pericarditis, sero-fibrinous pleurisy of the left pleural cavity, localized pleural effusion in a space between the upper and middle lobes of the right lung, osteoporosis of the sternum. The microscopical diagnosis was calcification of the aortic valves, chronic endocarditis and pericarditis of the left auricle, atheromatosis of the aortic cusp of the mitral valve, calcifying atherosclerosis of the intima of the thoracic part and of the intima and media of the abdominal part of the aorta, calcifying atherosclerosis of the splenic artery, adhesive pleurisy of the right pleural cavity, purulo-fibrinous pleurisy in the space between the upper and middle lobes of the right lung, chronic passive congestion of the lungs, atrophic induration of the liver, chronic passive congestion of the liver, atherosclerosis and passive congestion of the kidneys, renal infarction, passive congestion of the spleen and adrenal glands.

*Case 21* The anatomical diagnosis was extreme thrombosis and atherosclerosis of the left coronary artery, focal thrombosis and atherosclerosis of the right coronary artery, myocardial degeneration, healed and recent myocardial infarcts, adherent pericardium, fibrous pleurisy, anthracosis, emphysema, general arteriosclerosis, venous stasis of the liver, perisplenitis, perihepatitis, abdominal adhesions, hyperplasia of the spleen, arteriosclerosis of the kidneys, infarcts of the kidneys. The microscopical diagnosis was healed canalized thrombi and recent thrombosis of the coronary arteries, endocardial thickening, fibrosis and recent infarction of the left ventricle, atherosclerosis of the aorta, cyanotic atrophy of the liver, fibrous thickening of the pleura, anthracosis, perisplenitis, infarction of the kidneys, atherosclerosis of the kidneys.

*Case 28* The anatomical diagnosis was cardiac hypertrophy, chronic cardiac valvular disease (mitral and aortic), pericarditis, broncho-pneumonia, venous stasis of the organs. The microscopical diagnosis was chronic endocarditis, anemic infarcts of the heart, chronic passive congestion of the liver, passive congestion of the spleen, passive congestion of the kidneys, congestion and edema of the adrenal glands, normal aorta.

*Case 32<sup>4</sup>* The anatomical diagnosis was chronic endocarditis, mitral stenosis and aortic stenosis, cardiac hypertrophy and dilatation, sclerosis of the pulmonary artery, atelectasis of the lower and middle lobes of the right lung, healed bilateral apical tuberculosis, chronic passive congestion of the liver, spleen and kidneys, healed infarcts of the spleen and kidneys.

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<sup>4</sup> This report was obtained from another hospital and was not complete.

*Case 20* The anatomical diagnosis was calcification of the aortic valves, stenosis of the aortic valves, cardiac hypertrophy, advanced atherosclerosis of the aorta, moderate atheromatosis of the aortic cusp of the mitral valve and of the coronary vessels, arteriosclerosis of the kidneys, infarcts of the kidneys, cyanotic induration of the liver, passive congestion of the spleen and kidneys, ascites, edema of the legs and intestines, serous pericarditis, sero-fibrinous pleurisy of the left pleural cavity, localized pleural effusion in a space between the upper and middle lobes of the right lung, osteoporosis of the sternum. The microscopical diagnosis was calcification of the aortic valves, chronic endocarditis and pericarditis of the left auricle, atheromatosis of the aortic cusp of the mitral valve, calcifying atherosclerosis of the intima of the thoracic part and of the intima and media of the abdominal part of the aorta, calcifying atherosclerosis of the splenic artery, adhesive pleurisy of the right pleural cavity, purulo-fibrinous pleurisy in the space between the upper and middle lobes of the right lung, chronic passive congestion of the lungs, atrophic induration of the liver, chronic passive congestion of the liver, atherosclerosis and passive congestion of the kidneys, renal infarction, passive congestion of the spleen and adrenal glands.

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myxedema, and in many instances a very large part of the thyroid has been removed" Jordan (3) states that post-operative myxedema occurred in 0.9 per cent of a "primary hyperthyroidism" series of 533 cases treated by subtotal thyroidectomy and in 0.9 per cent of a "secondary hyperthyroidism" series of 320 cases treated by various types of partial thyroidectomy. Smith, Clute and Strieder (4), however, in a more recent (1928) publication from the same clinic, report that in 100 patients followed for 1 year or more after subtotal thyroidectomy, their incidence of post-operative myxedema has increased to 15 per cent. This they attribute to the recent practice of removing a larger portion of thyroid gland than formerly, and also to the post-operative use of iodine. Elliott (5), in a study of the results of thyroidectomy for toxic goiter, gives figures showing that of 74 cases undergoing a maximal subtotal thyroidectomy, 3 showed evidence of post-operative myxedema. Jordan, Smith, Clute and Strieder and Elliott do not state whether the myxedema was temporary or permanent.

The statistics of the Thyroid Clinic of the Massachusetts General Hospital indicate that following either x-ray treatment or subtotal thyroidectomy, *permanent* myxedema is a rare occurrence. A subtotal thyroidectomy in this hospital involves the removal of at least three-fourths and usually five-sixths to seven-eighths of the gland. Iodine has been used for several months post-operatively in many of the cases since the year 1924. The type of x-ray therapy used in the majority of instances was the exposure of both thyroid and thymus glands to about two-thirds the erythema dose. Treatments were usually given 3 to 4 weeks apart. During the period 1915-1926 inclusive, 465 cases of toxic goiter (for the most part exophthalmic goiter) were treated as follows:

130 by x-ray only

213 by subtotal thyroidectomy only, in one or more stages

122 by more limited operations, often with x-ray in addition, or else by subtotal thyroidectomy and x-ray combined

Only 8 cases of myxedema which was apparently permanent were observed among the above 465 cases, i.e., about 2 per cent. Five of these occurred after x-ray treatment, 1 after subtotal thyroidectomy,

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TABLE 1  
*Skeleton outlines of clinical and basal metabolic histories on the four uncharted cases of permanent myxedema following treatment for thyrotoxicosis*

| Case number | Description                   | Date                  | Basal meta-<br>bolic<br>rate<br><i>per cent</i> | Pulse | Weight<br><i>k gm</i> | Treatment                           | Clinical notes                           |
|-------------|-------------------------------|-----------------------|---|-------|-----------------------|-------------------------------------|--|
| 6           | Mr B S<br>Lab No 33<br>Age 24 | October 12, 1915      | +78   | 103   | 50.0                  |                                     | Exophthalmic goiter of 2 years' duration |
|             |                               | October 13, 1915      | +51   | 96    | 52.7                  | <i>First x-ray Treatment</i>        | Improved                                 |
|             |                               | June 5, 1916          | +1  | 73    | 60.0                  | <i>Steth x ray treatment</i>        | Well                                     |
|             |                               | July 5, 1916          |   |       |                       |                                     | Well                                     |
|             |                               | February 1, 1917      |   |       |                       |                                     | Well                                     |
|             |                               | April, 1919           |   |       |                       |                                     | Onset of symptoms of myxedema            |
|             |                               | May 5, 1919           | -14   | 56    | 59.0                  |                                     | Myxedema                                 |
|             |                               | September, 1920       |   |       |                       | Thyroid extract, grs IVss daily     | Much improved                            |
|             |                               | May 16, 1921          | -20   | 52    | 61.0                  |                                     |  |
|             |                               | June 1, 1921          | -8  | 60    | 58.5                  |                                     |  |
|             |                               | June 13, 1921         | -13   | 52    | 58.0                  | Thyroid increased to grs VIss daily | Well                                     |
|             |                               | September 19, 1921    | -1  | 54    | 57.5                  | Thyroid omitted                     |  |
|             |                               | March 20, 1922        |   |       |                       | Thyroid extract, grs IVss daily     |  |
|             |                               | March 30, 1922        | -15   | 49    | 56.5                  | Thyroid omitted                     |  |
|             |                               | About October 1, 1922 |   |       |                       |                                     |  |
|             |                               | October 12, 1922      | +9  | 60    | 56.0                  | Thyroid extract, grs IIIss daily    | Recurrence of myxedema                   |
|             |                               | June 21, 1923         | +2  | 56    | 56.9                  |                                     | No myxedema                              |
|             |                               | February 2, 1925      |   |       |                       |                                     | No myxedema                              |

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| Case number | Description                   | Date                  | Basal metabolic rate<br>per cent | Pulse | Weight<br>kgm | Treatment                           | Clinical notes                           |
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|             |                               | October 13, 1915      |                                  |       |               | First x-ray treatment               | Improved                                 |
|             |                               | June 5, 1916          | +51                              | 96    | 52.7          |                                     | Well                                     |
|             |                               | July 5, 1916          |                                  |       |               | Sixth x-ray treatment               | Well                                     |
|             |                               | February 1, 1917      | +1                               | 73    | 60.0          |                                     | Well                                     |
|             |                               | April, 1919           |                                  |       |               |                                     | Onset of symptoms of myxedema            |
|             |                               | May 5, 1919           | -14                              | 56    | 59.0          |                                     | Myxedema                                 |
|             |                               | September, 1920       |                                  |       |               | Thyroid extract, grs IVss daily     | Much improved                            |
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|             |                               | October 12, 1922      |                                  |       |               | Thyroid extract, grs IIIss daily    | Recurrence of myxedema                   |
|             |                               | June 21, 1923         | +9                               | 60    | 56.0          |                                     | No myxedema                              |
|             |                               | February 2, 1925      | +2                               | 56    | 56.9          |                                     | No myxedema                              |

TABLE 1—Continued

| Case number | Description                    | Date                                | Basal meta-bolic rate | Pulse | Weight | Treatment  | Clinical notes                             |
|-------------|--------------------------------|-------------------------------------|-----------------------|-------|--------|--|--|
|             |                                |                                     | per cent              |       | kgm    |  |  |
| 8           | Mrs D N<br>Lab No 40<br>Age 27 | November 9, 1915                    | +28                   | 103   | 55.8   | Diet and rest  | Exophthalmic goiter of 18 months' duration |
|             |                                | February 20, 1923                   | +44                   | 132   | 53.0   |  | Persistent thyrotoxicosis                  |
|             |                                | April 15, 1923                      | +34                   | 110   |        | <i>First x-ray treatment</i>                                     | Hemophilia Late syphilis                   |
|             |                                | April 30, 1923                      |                       |       |        |  |  |
|             |                                | September 10, 1924                  | +30                   | 94    | 64.0   | <i>Third x-ray treatment</i>                                     | Some improvement                           |
|             |                                | September 25, 1924                  |                       |       |        | Lugol's solution   | Myocardial failure                         |
|             |                                | September 26, 1924                  |                       |       |        |  |  |
|             |                                | September 30, 1924                  | +16                   | 62    | 63.0   | <i>Subtotal thyroidectomy</i>                                    |  |
|             |                                | October 8, 1924                     |                       |       |        | Lugol's omitted  |  |
|             |                                | October 15, 1924                    | -6                    | 80    | 61.0   |  | Well since operation                       |
|             |                                | November 26, 1924                   |                       |       |        |  | No thyrotoxicosis                          |
|             |                                | September 2, 1925                   |                       |       |        | X-ray treatment of spleen  | Secondary anemia                           |
|             |                                | September 12, 1925                  |                       |       |        |  | Menorrhagia                                |
|             |                                | October 14, 1925                    | -5                    | 84    | 61.5   | X-ray treatment of pelvis  | Well                                       |
|             |                                | January 4, 1926 to January 20, 1926 |                       |       |        |  | Menorrhagia                                |
|             |                                | April 21, 1926                      |                       |       |        |  | Well except for headaches                  |
|             |                                | June 5, 1926                        | -12                   | 78    | 63.9   | Lugol's solution   | No catamenia since January, 1926           |
|             |                                | June 21, 1926                       | -25                   | 68    | 64.8   |  | Myxedema                                   |
|             |                                | June 25, 1926                       |                       |       |        | Lugol's omitted Thyroid extract (Armour's) grs <i>IVss</i> daily |  |

TABLE 1—Continued

| Case number | Description                    | Date                                | Basal metabolic rate<br>per cent | Pulse | Weight<br>kgm | Treatment                                 | Clinical notes                             |
|-------------|--------------------------------|-------------------------------------|----------------------------------|-------|---------------|---|--|
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|             |                                | September 2, 1925                   |                                  |       |               | X-ray treatment of spleen                 | Secondary anemia                           |
|             |                                | September 12, 1925                  |                                  |       |               |   | Menorrhagia                                |
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|             |                                | June 21, 1926                       | -25                              | 68    | 64.8          |   | Myxedema                                   |
|             |                                | June 25, 1926                       |                                  |       |               | Lugol's omitted ex-tract (Armour's) daily | Thyroid grs IVss                           |

not disappear eventually as it did in case 11 (fig 6) Moreover, 3 of the cases have never been tested by omission of thyroid therapy for a length of time sufficient to ascertain whether or not the myxedema would recur

The diagnosis of myxedema was definite in all the cases except no 8 (table 1) She had no noticeable edema, but her subjective symptoms

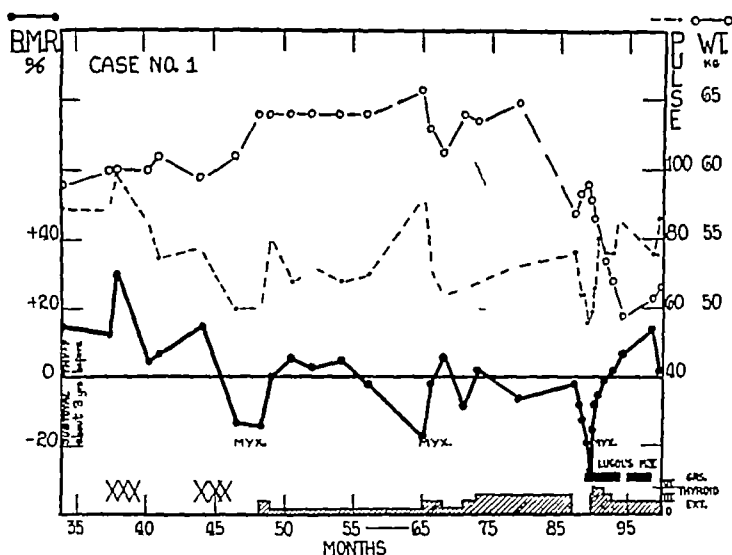


FIG 1 LAB NO 1505 MISS F F T AGE 47 PERMANENT MYXEDEMA OCCURRING WITHIN 3 MONTHS AFTER X-RAY THERAPY (X) PRECEDED BY SUBTOTAL THYROIDECTOMY (ABOUT 3 YEARS BEFORE FIRST METABOLISM DETERMINATION) FOR EXOPHTHALMIC GOITER

Marked exophthalmos persists to date Maintenance dose of thyroid extract is 3 grains daily In this and subsequent charts, black areas denote Lugol's medication, and cross-hatched areas, thyroid medication

were characteristic and disappeared on thyroid therapy Case 2 (fig 2)<sup>6</sup> is typical of the group, and, when myxedematous, presented the following signs and symptoms

She was dopey, lacked energy, had a poor appetite, fatigued very easily and felt cold all the time She had dyspnea on exertion Her speech was slow and thick

<sup>6</sup> We wish to thank Dr E P Richardson for the use of the data on this case

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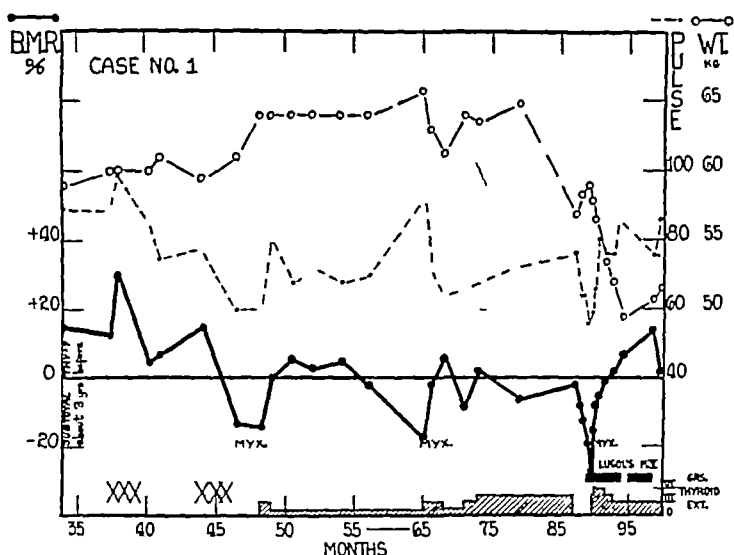


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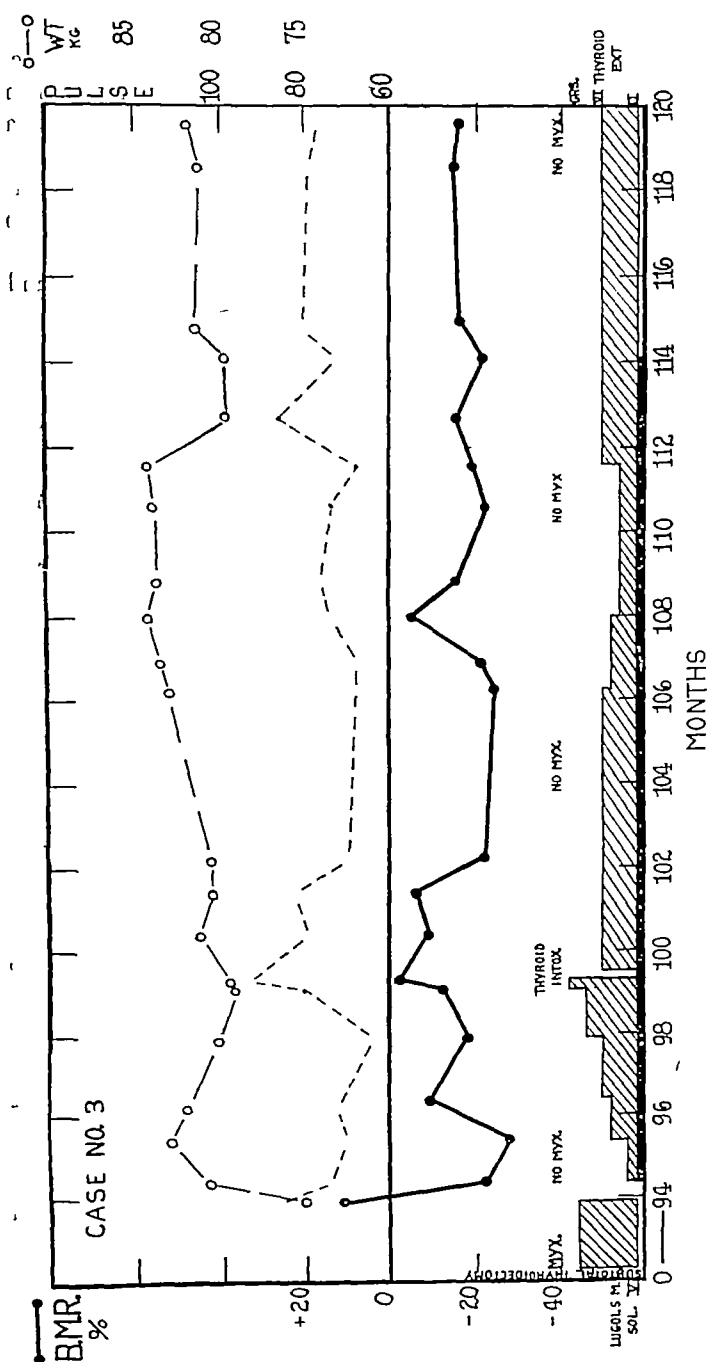


FIG 3 LAB No 3947 Mr R C P AGE 49 COMBINED MYXEDEMA AND NORMAL LOW BASAL METABOLIC RATE FOLLOWING SUBTOTAL THYROIDECTOMY FOR EXOPHTHALMIC GOITER

The myxedema occurred within 6 months after the thyroidectomy. The patient's metabolism remained low in spite of 6 grains of thyroid extract (BW) daily, but there were no symptoms of myxedema. Raising his metabolism to standard normal by a dose of 12 grains daily produced thyroid intoxication.

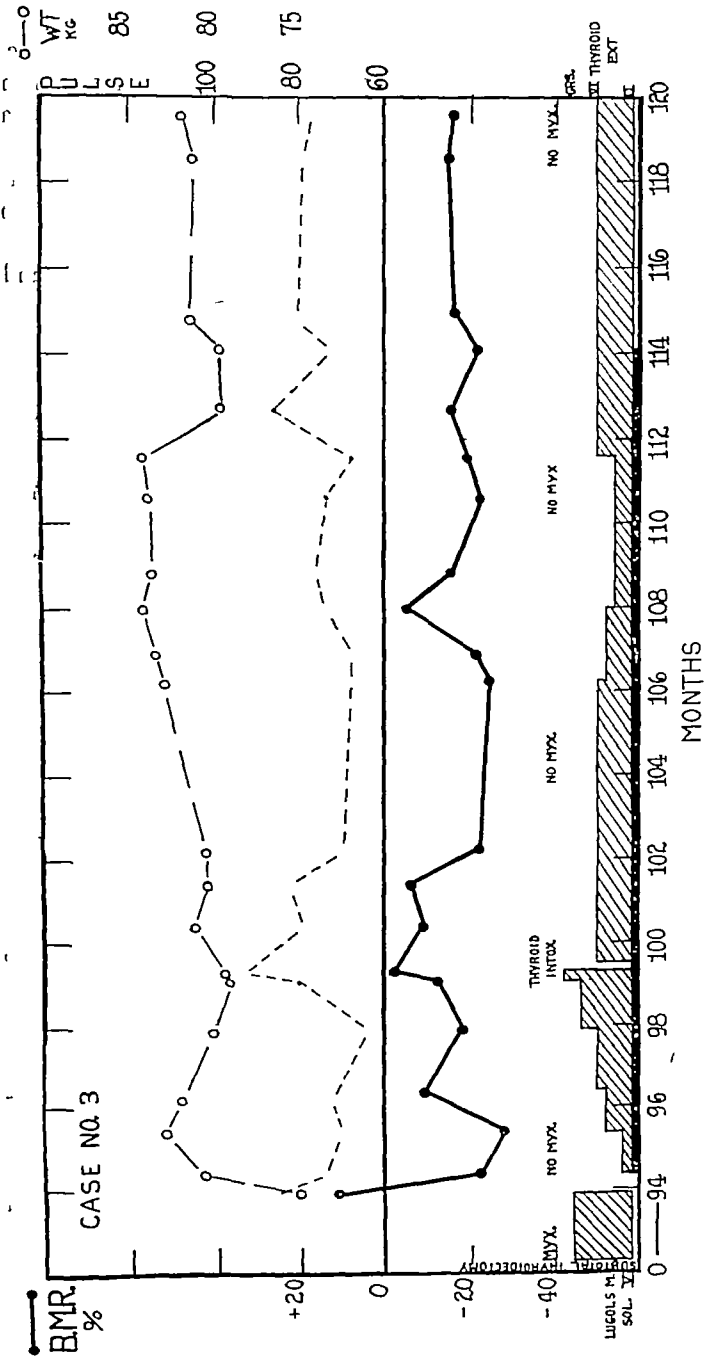


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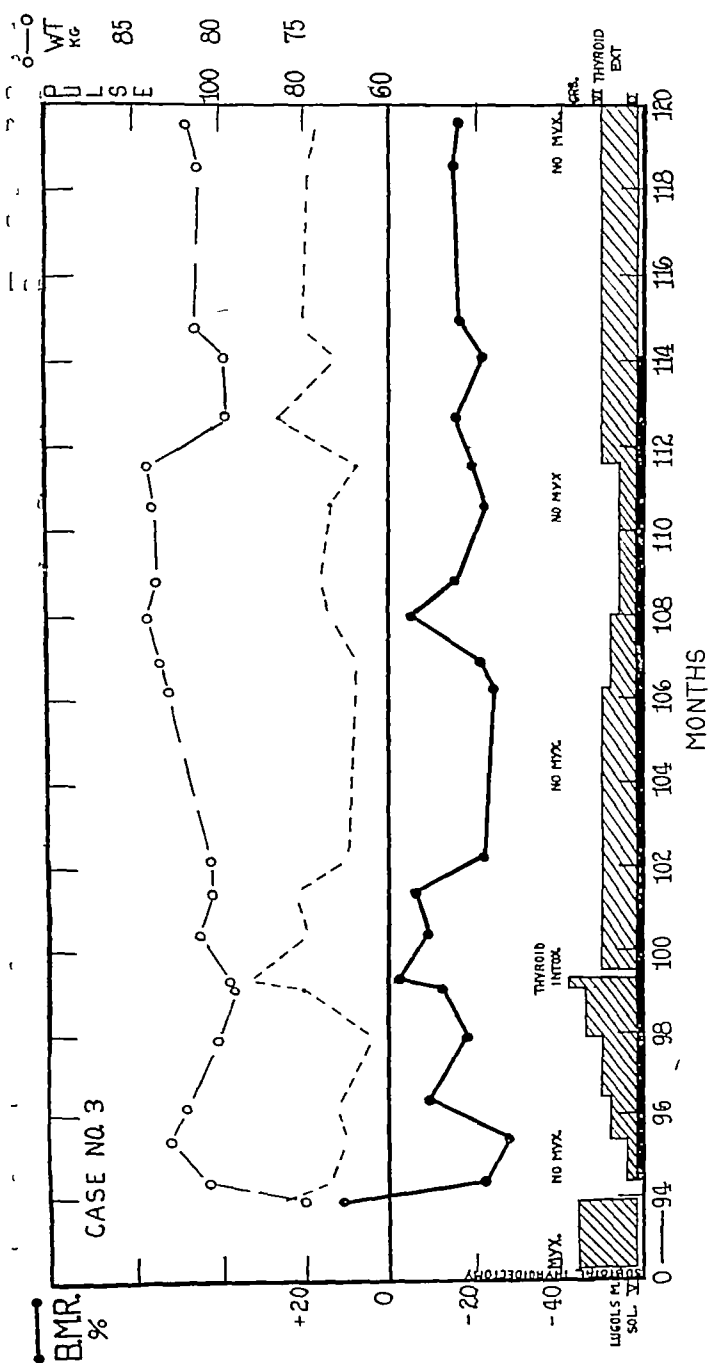


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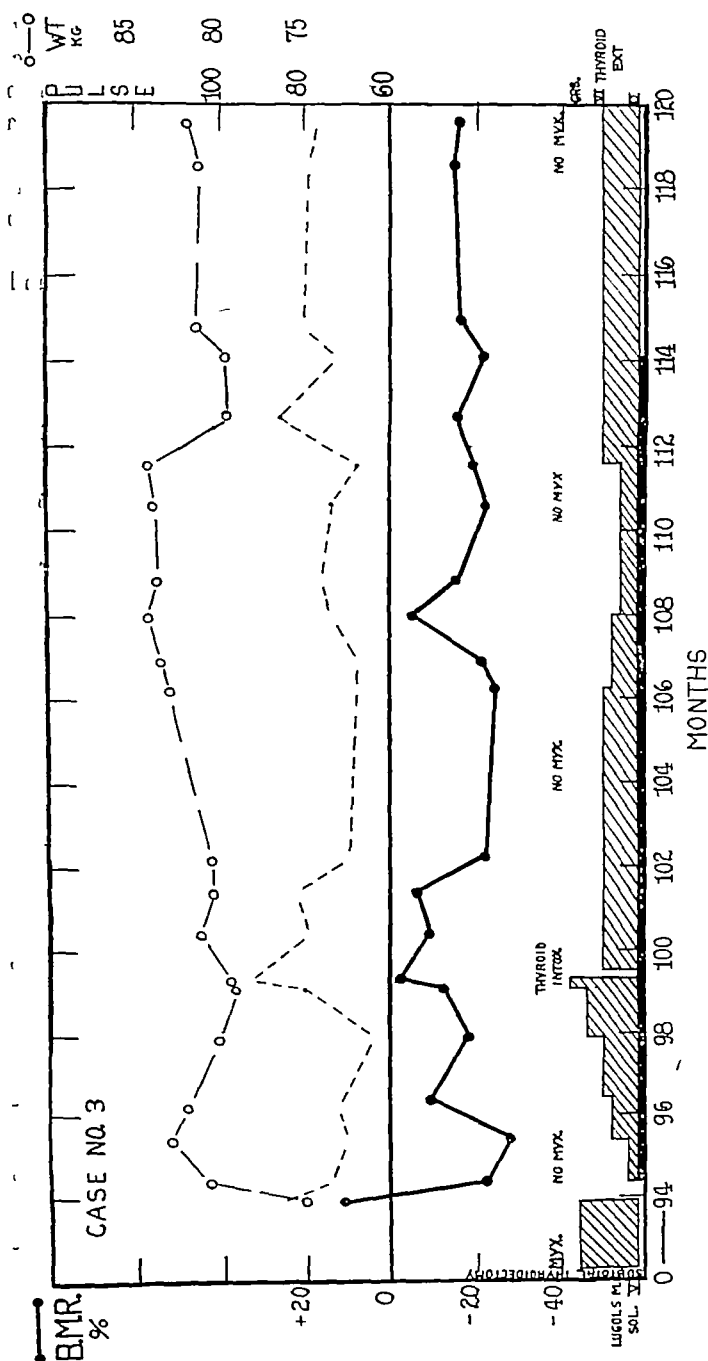


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*C Late onset after x-ray therapy*

One of the most striking features brought out by a study of these cases was the late onset of the myxedema after x-ray therapy for thyrotoxicosis. This has been previously noted by Means and Holmes

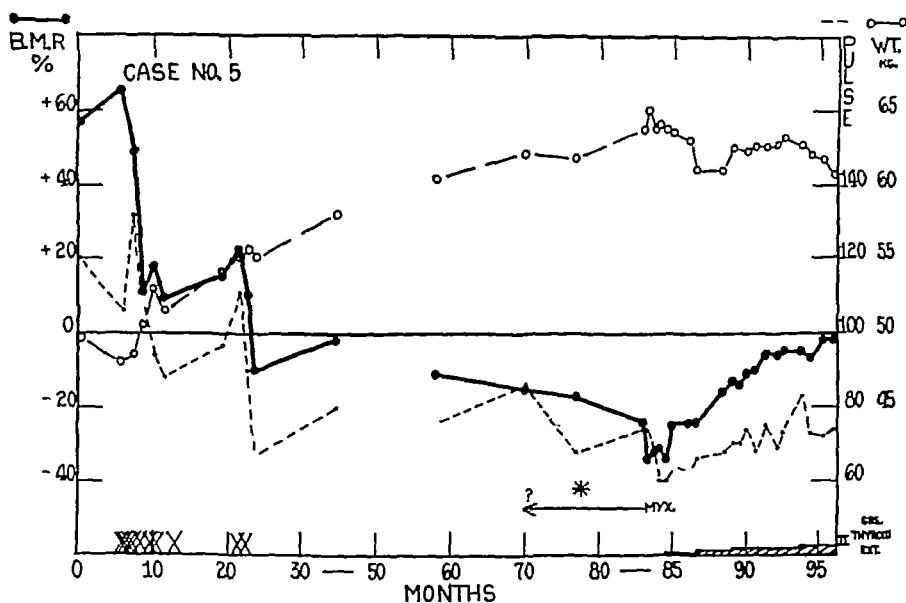


FIG 5 LAB No 628 MRS M J AGE 41 ONSET OF MYXEDEMA 3 TO 5 YEARS AFTER X-RAY THERAPY (X) FOR TOXIC GOITER

Symptoms noted shortly before radiation and removal of left breast for carcinoma (\*) The patient is well and has a standard normal metabolic rate on  $1\frac{1}{2}$  grams of thyroid extract daily

(8) in two patients In the 5 cases thus treated, the times of onset were as follows

| Case        | Years after last x-ray treatment |
|-------------|----------------------------------|
| 2 (fig 2)   | 4 to 5                           |
| 4 (fig 4)   | 5 to 8                           |
| 5 (fig 5)   | 3 to 5                           |
| 6 (table 1) | 4                                |
| 7 (table 1) | 2 to 6                           |

(In this connection, it is of interest that the onset of myxedema in the case of temporary myxedema following x-ray therapy was also late,

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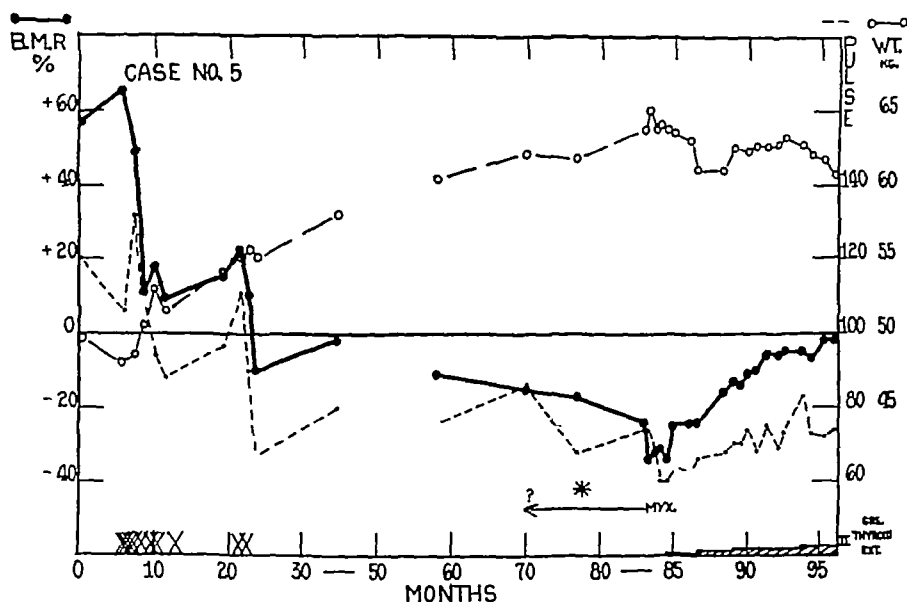


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(In this connection, it is of interest that the onset of myxedema in the case of temporary myxedema following x-ray therapy was also late,

When next seen in this hospital in June, 1909, she was taking thyroid, but irregularly. Her goiter and exophthalmos had disappeared. She had no edema, her speech was normal and her facial expression "only suggestive, but not characteristic of myxedema." Her tongue was large, her hair and skin were dry and she felt chilly. She began taking thyroid regularly and felt better. In December, 1910, it was regulated at 5 grains (Burroughs Wellcome) daily.

In the next nine years, she underwent four operations in other hospitals, two for removal of Fallopian tubes, ovaries and uterus on account of menorrhagia, and two for herniae in the scars. During this time, whenever thyroid extract was omitted she became myxedematous again. In January, 1920, at the time of her last operation, a high blood pressure was noted. Her dose of thyroid varied from 2 to 4 grains daily for some time thereafter. In April, 1926, she was in another hospital because of a recurrence of her myxedema. She had her first basal metabolism determination, which was minus 28 per cent. She was discharged improved on 3 grains of thyroid extract daily.

In September, 1926, she returned to this hospital because of failing vision. She stated that she was taking 8 grains of thyroid (unknown brand) daily, but this was doubtful in view of her symptoms. She looked myxedematous. Her face was puffy. She was lethargic and always tired and sleepy. Her voice was hoarse, her tongue large, her hair coarse and her skin dry. Her heart was enlarged and her blood vessels somewhat sclerosed. Her blood pressure was  $\frac{238}{130}$ . Her basal

metabolism was plus 3 per cent and her pulse rate 80. Thyroid was omitted until December 1926, during which time her metabolism fell to minus 20 per cent, and her signs and symptoms became so pronounced that there was no doubt about the diagnosis of myxedema. She had the high protein concentration in her spinal fluid and the albuminuria so often present in this disease (9). She improved on gradually increasing doses of Armour's thyroid extract. The albuminuria disappeared and the protein content of the spinal fluid decreased markedly on this medication (9). Four grains daily, however, produced symptoms of thyroid intoxication, viz., nausea, vomiting, precordial and epigastric pain and palpitation. These disappeared when thyroid was omitted for a short time. A dose of 2 grains daily was resumed. This dose proved satisfactory, and maintained her metabolism at a normal level for several months. There were no signs nor symptoms of myxedema, and she felt as well as could be expected in view of her hypertension. After a time, however, she developed marked precordial pain and palpitation with a basal metabolic rate of plus 26 per cent. It was again necessary to stop the administration of thyroid extract. Her myxedema recurred. After an interval of 5 months, 3 grains of Armour's thyroid daily was started, but in a few days caused a recurrence of her precordial pain. The dose was finally regulated at  $\frac{1}{2}$  grain of Armour's thyroid daily. This has maintained the basal metabolic rate at a normal level, has caused no precordial pain, and her myxedema has not recurred.

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basal metabolism in the two cases in which the diagnosis of myxedema appeared to be definite, are given below

*Case 11* (fig 6) Lab No 348<sup>9</sup> Mrs M B Age 38 In September, 1920, 8 months after 6 x-ray treatments (ending in January, 1920) for toxic goiter, she was clinically well and had a basal metabolism of minus 3 per cent In February, 1921, her metabolism was still normal, and the only symptom present was numbness of the hands She looked somewhat pale and her skin was a little dry In August, 1921, 1½ years after the x-ray treatment, her metabolic rate was down to minus 35 per cent There had been a weight gain of 9 kgm since 1920 She had not been well for 3 months She complained of numbness of her hands, general weakness, pains in her legs on climbing stairs, and marked constipation She felt cold and did not perspire during the hot days She appeared dull Her face was expressionless, her speech slow and her skin dry and coarse Her lips were bluish and her face and conjunctivae pale A diagnosis of myxedema was made

Thyroid extract was started This produced marked improvement and raised her metabolism to standard normal by September, 1921 On two subsequent occasions, one in June, 1922, and one in August, 1922, when she omitted thyroid for 3 weeks, her rate fell to minus 23 per cent each time, and she became tired and slowed up Her skin became dry and her face expressionless again She resumed thyroid and felt perfectly well On November 9, 1926, at which time her metabolism was minus 11 per cent, thyroid was omitted Her metabolic rate gradually fell, until by March, 1927, it was minus 23 per cent Until June, 1928, a period of 1½ years from the time thyroid was omitted, it ranged from minus 8 to minus 22 per cent, with one observation of zero There was no return of symptoms of myxedema Her hair and skin did not become drier There was no evidence of edema and no decrease in strength and energy She was not slowed up, never felt like sleeping in the daytime, and could do all her own housework without fatigue, rising at 6 a m and retiring at 9 to 10 p m She looked well and insisted that she felt just as well, if not better, than when taking thyroid extract

*Case 12* (fig 7) Lab No 2940<sup>10</sup> Mrs E B C Age 48 This patient had a subtotal thyroidectomy for exophthalmic goiter on December 10, 1924 Up to March, 1925, her basal metabolism ranged from minus 10 to minus 16 per cent and she was exceptionally well By May, 1925, her metabolic rate was minus 25 per cent Her memory was failing and she was becoming weak and lethargic Her

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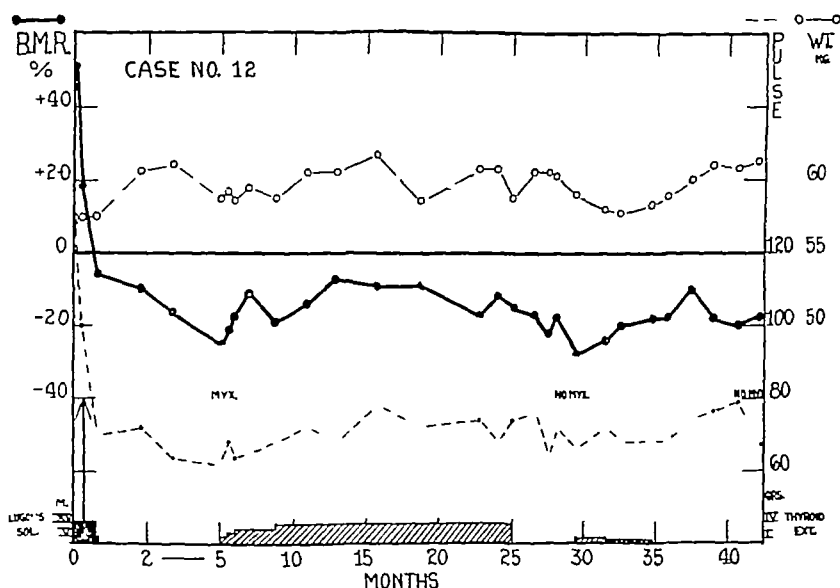


FIG 7 LAB No 2940 MRS E B C AGE 47 ONSET OF TEMPORARY MYXEDEMA 4 TO 5 MONTHS AFTER SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

For 4 months after first omission, and  $7\frac{1}{2}$  months after last omission of thyroid extract, the patient has remained healthy. Her basal metabolic rate is low, but apparently this is normal for her.

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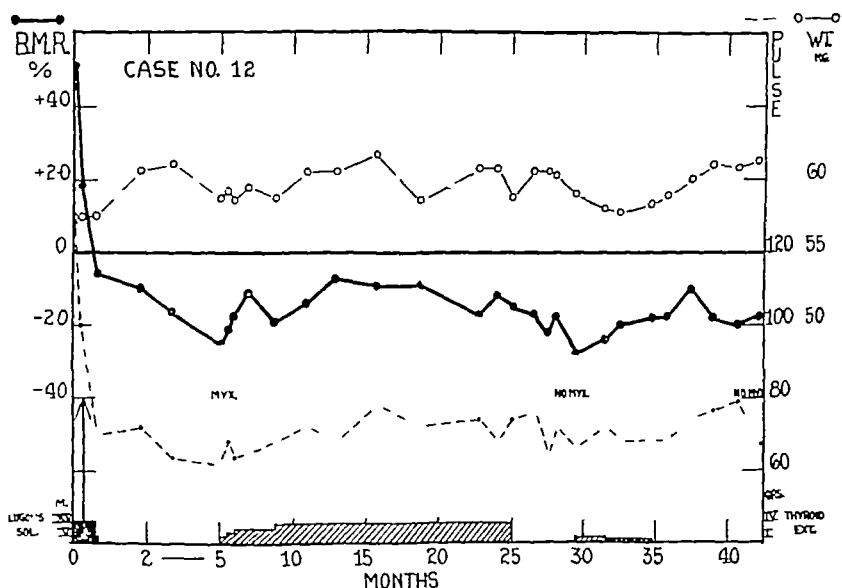


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that of myxedema following subtotal thyroidectomy, i e., about 1 per cent whereas, after x-ray, the incidence was about 4 per cent This suggests that x-ray had a definite influence in causing the myxedema in our series The number of cases on which these figures are based however, is necessarily so small that one cannot place much reliance upon such apparent differences in incidence In any event, the incidence of myxedema following x-ray therapy of the thyroid is not great enough to constitute a contraindication to this form of treatment

If the myxedema be an x-ray effect, it is similar in its late onset to such other x-ray effects as skin atrophy and telangiectasis, and is probably due to a very slow fibrosis of the thyroid gland tissue Skin and gland changes do not go hand in hand however In only one case of this series was there any evidence of skin changes Case 4, treated in the year 1916 before the technique was perfected, shows a small amount of telangiectasis Thus, if the myxedema be due to x-ray therapy, sufficient dosage to destroy thyroid tissue in 5 cases, affected the skin over the gland in only one case On the other hand, we have a patient first treated in the year 1915 who now shows considerable telangiectasis, but who still has thyrotoxicosis If the change produced in the gland is in the nature of a gradual fibrosis, it evidently does not preclude a restoration of gland function at a later date, as shown by case 11 (fig 6), where myxedema occurred over a year after x-ray treatment and persisted for at least 1 year, but did not recur up to  $1\frac{1}{2}$  years after omission of thyroid extract Another x-ray effect which might be considered comparable to this is that of restoration of function of the ovaries after it has been suspended by x-ray treatment Here, however, the onset of the ovarian deficiency is immediate, and not delayed, as may be the onset of thyroid deficiency

The fact that the myxedema may be temporary has an important bearing upon thyroid therapy It shows the desirability of periodic omissions of this medication in order to prevent unnecessary administration, in a certain number of cases

#### SUMMARY AND CONCLUSIONS

1 Myxedema following treatment for thyrotoxicosis may be either temporary or permanent

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often seen. After about 20 hours, or sometimes earlier if a meal of meat is eaten, the dogs become definitely ill, refuse to move about unless urged, and usually have fibrillary tremors which can be felt in most of the skeletal muscles. Visible twitching of the paws and lips soon follows and becomes more marked during the next 12 hours. Violent general convulsions are sometimes seen, especially when aroused by some outside stimulus such as handling. At this stage a foul bloody diarrhea is frequently seen with vomiting of black material containing changed or even fresh blood. The dogs then grow gradually weaker and the convulsive twitching becomes more feeble or disappears. There may be coma, but more often there is a profound weakness with consciousness retained. Death most often occurs between 48 and 60 hours after the dose and is usually from weakness or exhaustion but occasionally comes suddenly in the midst of a convulsive seizure. Convulsive symptoms are occasionally entirely absent and death follows a period of depression and coma.

As has been previously noted by Lamson (1), Meyer and Pessoa (3), and Davis (4), the most obvious damage done by carbon tetrachloride is to the liver. At autopsy this organ appears yellowish and the lobules are definitely outlined with red central areas surrounded by yellow tissue. On section this same appearance is seen throughout the tissue. The liver feels very greasy and is so soft and friable that it can be readily mashed in the fingers. Sometimes the lobes contain cracks from which loss of blood into the peritoneal cavity may have reached the proportion of severe hemorrhage. This finding is most common in the type of death mentioned above which ensues rapidly in the midst of a convulsive seizure. In such cases as much as a liter of blood may be found in the abdominal cavity and this hemorrhage is apparently the immediate cause of death. More commonly, however, the liver though congested and friable is not ruptured. The gastro-intestinal tract usually contains old blood and sometimes fresh blood is seen oozing from numerous hemorrhagic areas in the pyloric end of the stomach and upper third of the small intestine. Congestion in these portions of the tract is very marked and is not due to the local irritation of carbon tetrachloride since the same doses of the drug cause no such condition in adequately protected animals. The kidneys show no very striking abnormality though some congestion is often noted.

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by the early administration of calcium the majority of dogs can be cured by persistent medication during the 3 or 4 days of severe intoxication

Typical protocols of 2 of about 25 dogs cured by calcium therapy serve to illustrate the usual course of treatment. The first dog reported required medication somewhat longer than is usually necessary after receiving 4 cc of carbon tetrachloride per kilogram. The case is otherwise perfectly typical and is chosen for presentation here because it illustrates the use of several forms of calcium therapy. The second dog required less persistent treatment but in other respects is very similar to the first one. Later work has shown the inadvisability of allowing poisoned or convalescent dogs to eat meat but this point was not appreciated at the time of these particular experiments

*Protocol, Case T D 11* Brindle and white male, weight 7.9 kgm. On low calcium meat diet 2 to 3 weeks before experiment

January 22, 1927

3 00 p.m. Received 4 cc  $\text{CCl}_4$  per kilogram by stomach tube—total dose 31.6 cc

January 23, 1927

9 00 a.m. Has slight twitching of paws and lips

10 00 a.m. Given 100 cc of 5 per cent calcium lactate by stomach tube

2 00 p.m. Appears very sick, breathing irregularly due to spasmodic contractions of the diaphragm

6 00 p.m. Has violent tetanic convulsions. Given 500 mgm of  $\text{CaCl}_2$  intravenously as 5 per cent solution

6 30 p.m. Seems much better—convulsions have ceased entirely

8 00 p.m. Dog is perfectly quiet, conscious but weak

9 00 p.m. Slight muscular twitching reappears. Given 350 mgm of  $\text{CaCl}_2$  intravenously as 1 per cent solution. Dog vomited undigested meat eaten two days before

10 00 p.m. Seems much better, walks around the room, has no tremor

January 24, 1927

10 00 a.m. Seems rather weak but has no convulsive symptoms. Given 100 cc of milk and 100 cc 5 per cent calcium lactate by stomach tube

2 00 p.m. Condition unchanged. Given 150 cc of milk, 100 cc 5 per cent calcium lactate by stomach tube

8 00 p.m. Condition unchanged. Given 150 cc of milk, 100 cc 5 per cent calcium lactate by stomach tube

January 25, 1927

9 00 a.m. Has fine tremor in paws. Given 100 cc of milk, 50 cc 5 per cent calcium lactate and 1 egg by stomach tube

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*Protocol, Case T D 32* Weight 7.8 kgm On low calcium meat diet for 3 weeks before experiment

February 28, 1927

3 00 p.m. Given 4 cc  $\text{CCl}_4$  per kilogram by stomach tube—total dose 31.2 cc

8 00 p.m. Resting quietly

March 1, 1927

9 00 a.m. Good condition

10 00 a.m. Given 50 cc molar  $\text{NH}_4\text{Cl}$  by stomach tube

2 00 p.m. Given 50 cc molar  $\text{NH}_4\text{Cl}$  by stomach tube

3 30 p.m. Given 100 cc 5 per cent calcium lactate, 100 cc of milk and 1 egg by stomach tube

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March 2, 1927

9 00 a.m. Fair condition Given 30 cc molar  $\text{NH}_4\text{Cl}$ , 175 cc of milk and 1 egg by tube—vomited

12 15 p.m. Dog lying on side with violent muscle twitching—is only semi-conscious Given 450 mgm  $\text{CaCl}_2$  intravenously as 5 per cent solution The twitching stops within 20 minutes and the dog stands up apparently normal

8 00 p.m. Still in good condition Given 50 cc 5 per cent calcium lactate and 100 cc of milk by stomach tube

10 00 p.m. The eight o'clock medication was repeated

March 3, 1927 Dog in good condition Has good appetite and eats a meal of meat, bread, a little milk and 5 grams of a mixture of calcium lactate and carbonate

March 4, 1927 Dog in good condition Eats well, apparently normal

March 5, 1927 Discharged

Of more practical interest than the treatment of poisoned animals is the highly protective action of a preliminary course of a diet high in calcium This is obtained by the daily addition of about 5 grams of a mixture of calcium carbonate and lactate to the meat diet for 1 to 3 weeks before giving carbon tetrachloride From a total of 105 dogs on a low calcium meat diet used for various experiments, 84 died with typical symptoms following 4 cc of carbon tetrachloride per kilogram Of the 21 surviving, 6 were desperately ill for several days, 6 refused to eat meat after the administration of carbon tetrachloride, and 9 showed no serious symptoms In contrast to this 75 from a total of 95 on a diet of meat and calcium salts showed no serious symptoms

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March 2, 1927

9 00 a.m. Fair condition Given 30 cc molar  $\text{NH}_4\text{Cl}$ , 175 cc of milk and 1 egg by tube—vomited

12 15 p.m. Dog lying on side with violent muscle twitching—is only semi-conscious Given 450 mgm  $\text{CaCl}_2$  intravenously as 5 per cent solution The twitching stops within 20 minutes and the dog stands up apparently normal

8 00 p.m. Still in good condition Given 50 cc 5 per cent calcium lactate and 100 cc of milk by stomach tube

10 00 p.m. The eight o'clock medication was repeated

March 3, 1927 Dog in good condition Has good appetite and eats a meal of meat, bread, a little milk and 5 grams of a mixture of calcium lactate and carbonate

March 4, 1927 Dog in good condition Eats well, apparently normal

March 5, 1927 Discharged

Of more practical interest than the treatment of poisoned animals is the highly protective action of a preliminary course of a diet high in calcium This is obtained by the daily addition of about 5 grams of a mixture of calcium carbonate and lactate to the meat diet for 1 to 3 weeks before giving carbon tetrachloride From a total of 105 dogs on a low calcium meat diet used for various experiments, 84 died with typical symptoms following 4 cc of carbon tetrachloride per kilogram Of the 21 surviving, 6 were desperately ill for several days, 6 refused to eat meat after the administration of carbon tetrachloride, and 9 showed no serious symptoms In contrast to this 75 from a total of 95 on a diet of meat and calcium salts showed no serious symptoms

TABLE 1

*Icteric indices determined\* before and at intervals after administration of 4 cc of CCl<sub>4</sub> per kilogram to dogs on high and low calcium meat diets*

| Number of dog         | Indices observed at indicated time intervals |            |          |          |          | Final outcome      |
|-----------------------|--|------------|----------|----------|----------|--------------------|
|                       | Before dose                                  | After dose |          |          |          |                    |
|                       |  | 24 hours   | 48 hours | 72 hours | 96 hours |                    |
| Low calcium—meat diet |  |            |          |          |          |                    |
| 27-10-3               | 0  |            | 16 8     |          |          | Died 120 hours     |
| 27-10-16              | 0  | 3 0        |          |          |          | Died 36 hours      |
| 27-10-18              | 0  | 5 0        |          |          |          | Died 40 hours      |
| 27-11-14              | 0  | 9 0        |          |          |          | Died 35 hours      |
| 27-11-15              | 0  | 6 6        | 10 6     |          |          | Died 48 hours      |
| 27-11-16              | 0  | 7 0        | 9 3      |          |          | Died 48 hours      |
| 27-11-18              | 0  | 11 1       |          |          |          | Died 25 hours      |
| 27-11-27              | 0  | 10 4       |          |          |          | Died 24 hours      |
| 27-11-29              | 0  | 3 0        | 5 8      |          |          | Died 70 hours      |
| T D 68                | 0  | 3 1        | 2 6      | 6 6      |          | Died 90 hours      |
| T D 71                | 0  | 1 0        | 3 5      |          |          | Died 70 hours      |
| T D 74                | 0  | 1 5        | 10 4     |          |          | Died 60 hours      |
| T D 75                | 0  | 2 5        | 7 6      |          |          | Died 49 hours      |
| T D 76                | 0  | 2 0        | 8 0      |          |          | Died 50 hours      |
| T D 46                | 0  | 2 5        | 9 0      |          |          | Died 49 hours      |
| T D 45                | 0  | 2 7        | 14 0†    |          |          | Died 33 hours      |
| T D 59                | 0  |            | 14 3     | 20 8†    |          | Died 60 hours      |
| T D 61                | 0  | 2 0        | 19 3     | 23 6     |          | Died 80 hours      |
| T D 62                | 0  | 8 2        | 13 7     |          |          | Died 54 hours      |
| T D 63                | 0  | 5 2        | 7 5      |          |          | Died 26 hours      |
| L T 22                | 0  | 1 0        | 5 5      | 7 7      | 15 0     | Died 110 hours     |
| L T 23                | 0  | 2 7        | 7 2      |          |          | Died 48 hours      |
| L T 26                | 0  | 1 0        | 4 6      | 26 0     | 25 0     | Died 98 hours      |
| 28-6-3                | 0  | 6 3        | 12 1†    |          |          | Died 36 hours      |
| 28-6-4                | 0  | 1 0        | 2 0      | Trace    |          | Recovered          |
| 27-10-17              | 0  | 0          | 1 0      |          |          | Recovered          |
| 27-9-1                | 0  |            | 7 0      | 7 0      | 3 5      | Recovered          |
| 29-9-2                | 0  |            | 4 0      | 3 2      | 0        | Recovered          |
| 28-6-1                | 0  | 2 8        | 8 2      | 2 8      |          | Recovered          |
| 28-6-2                | 0  | 1 5        | 3 5      | 2 0      |          | Recovered          |
| 27-11-23              | 0  | 4 5        | 14 0     |          |          | Killed for tissues |
| 27-11-13              | 0  | 8 4        | 12 0     |          |          | Killed for tissues |
| 27-11-28              | 0  | 5 5        | 7 8      |          |          | Killed for tissues |

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| Number of dog         | Indices observed at indicated time intervals |            |          |          | Final outcome |                    |
|-----------------------|--|------------|----------|----------|---------------|--------------------|
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|                       |  | 24 hours   | 48 hours | 72 hours |               | 96 hours           |
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| 27-11-27              | 0  | 10 4       |          |          |               | Died 24 hours      |
| 27-11-29              | 0  | 3 0        | 5 8      |          |               | Died 70 hours      |
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| 28-6-4                | 0  | 1 0        | 2 0      | Trace    |               | Recovered          |
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of any clean-cut difference in the degree of derangement of these functions in the two groups. Some cases show a retention of phenol-tetrachlorophthalein but these are as likely to be found in one group as the other. Furthermore, although there is a very definite decreased tolerance for levulose in the majority of cases which have received carbon tetrachloride there is a disappointing lack of parallelism between the severity of symptoms and the degree of hyperglycemia produced by the ingestion of a given amount of levulose.

*Blood chemistry a Bilirubinemia* The determination of bilirubin in the blood serum either by van den Bergh's method (7) or more simply by the determination of the icteric index by a modification of Bernheim's technique (8) furnished data more nearly parallel with the severity of symptoms. In table 1 are presented icteric indices determined at intervals after carbon tetrachloride administration to dogs in the high and low calcium groups described above. In general the bilirubinemia tends to be much more severe in the animals on low calcium diet than in those protected by high calcium. Exceptions to this rule are usually seen in the occasional unexplained atypical cases in each group. The retention of bile pigments begins to be noticeable 12 to 20 hours after the dose of carbon tetrachloride, and usually as the bilirubinemia becomes severe the more acute symptoms appear. The reason for the lower concentration of bilirubin in the blood of animals on high calcium diets is still unexplained. An observation which suggests a possible theory is the much greater tendency for the *tissues* of high calcium animals to appear jaundiced. It may be possible that tissues well laden with calcium tend to hold bilirubin, perhaps in combination with calcium, preventing its accumulation in the blood stream.

*b Blood calcium determinations*<sup>1</sup> The total blood calcium levels of normal dogs determined by Clark and Collip's modification of Tisdall's method (9) showed no consistent differences in the two groups and ranged between 10.5 and 12.0 mgm per 100 cc of serum. During severe intoxication there is no significant change in the total calcium concentration. The figures are within normal limits with a tendency in many cases to average slightly higher than the preliminary level before receiving carbon tetrachloride. No data have yet been obtained regarding possible changes in the ionized fraction of the total

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Briefly summarized, the intoxication produced by carbon tetrachloride in susceptible animals is characterized by gastro-intestinal irritation, nervous disturbances and convulsions, followed by weakness, depression, and death. There is a retention of bile pigments in the blood and a more or less severe hypoglycemia. These symptoms are aggravated by eating meat and may be prevented or cured by the administration of calcium salts

*Points of similarity between carbon tetrachloride intoxication and experimental guanidine poisoning*

The foregoing pathological picture calls to mind similar ones described in the literature as typical of guanidine poisoning. As early as 1876 Gergens and Baumann (16) described the effect of intravenous injections of guanidine sulphate in frogs and mammals. Dogs and rabbits showed weakness, fibrillary twitching of muscles, convulsions and death following injection. Putzeys and Swaen (17), Fuhner (18) (19) Camis (20) and others contributed numerous studies on the action of guanidine compounds on various parts of the nervous system and on the skeletal musculature of frogs—Fuhner bringing out the antagonism which exists between the actions of calcium salts and guanidine on these structures. More extensive mammalian experiments were reported by Watanabe (21) (22) (23) (24) (25) in a series of papers in which he again described the nervous symptoms, studied nitrogen metabolism, and reported that a severe hypoglycemia was induced. This he ascribed to a condition of acidosis which he believed was indicated by increased ammonia excretion in the urine. Gyorgy and Vollmer (26) however discredited the acidosis theory and found rather a condition of alkalosis and reported that the symptoms of guanidine intoxication can be relieved by the administration of hydrochloric acid either intravenously or by mouth. Paton and Findlay (27) studied the intoxication produced by guanidine or methyl guanidine and described symptoms very similar to the tetany seen after parathyroidectomy and believed that the two conditions are identical. Perhaps the most complete pharmacological and toxicological study of guanidine compounds which we have is a paper

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from normal during intoxication is increased rather than decreased by the correction. Since we wished to keep the volume of blood required for each determination as small as possible in order to make repeated studies on the same animal at short intervals—these corrections were not applied except in a few preliminary observations. The figures given in table 3 are the uncorrected values obtained. We therefore make no claim for their absolute accuracy within 0.2 to 0.3 mgm per 100 cc of blood. We know the values are as a rule slightly high. We do however make the point that the rise in color producing substances occurs without a corresponding increase in blood constituents other than guanidine known to give color with the reagent used. We believe this rise to be due to an accumulation of guanidine compounds in the blood.

A description of our exact procedure which is practically that of Major and Weber (35) follows. 10 cc of oxalated blood are precipitated in a 100 cc volumetric flask by the Folin-Wu (37) method for protein precipitation with the single difference that  $2/3$  N hydrochloric acid is used in place of  $2/3$  N sulphuric acid. Fifty cubic centimeters of the protein free filtrate are evaporated slowly to dryness on a hot plate or steam bath. The dry residue is then extracted repeatedly with small amounts of hot absolute alcohol with careful loosening of the residue with a rubber policeman to insure complete extraction of guanidine. The successive alcoholic extracts are filtered through a small filter and the total of 30 to 40 cc of filtrate collected in a small beaker and evaporated just to dryness on a hot plate. Care should be exercised not to char the residue. The residue in the beaker is then dissolved in 5 cc of distilled water and to this solution 1 cc of the freshly prepared guanidine reagent described above is added. If the resulting colored solution is not perfectly clear it is shaken with a little powdered barium carbonate and filtered through a small high grade filter paper. The clear filtrate is allowed to stand 15 minutes and compared in a colorimeter with an appropriate standard solution of guanidine hydrochloride treated with the same reagent. Fifty cubic centimeters of protein free filtrate representing 5 cc of normal blood usually require a standard containing 0.02 mgm of guanidine (calculated as guanidine) in 6 cc. Abnormal bloods may require standards as high as 0.2 mgm in the same volume.

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The results in table 2 show the accuracy of this procedure in determining guanidine in pure solutions, normal blood, and in blood to which increased amounts of interfering substances have been added.

From these figures it appears that only in extreme nitrogen retention could the apparent increase in guanidine be attributed to the interference of the usual blood constituents. In repeated tests made by us and in an earlier rather extensive study by Lamson (1) no such retention was found in carbon tetrachloride poisoning.

*Determination of guanidine and sugar levels in blood of dogs during carbon tetrachloride and chloroform poisoning and after guanidine administration*

The method just described was applied to the study of blood samples taken before and at intervals after the administration of carbon tetrachloride to dogs under various conditions which are known to affect the toxicity of the drug. These figures, together with blood sugar and icteric index determinations on the same samples, are arranged in groups in table 3 and are discussed separately under appropriate headings.

*Carbon tetrachloride poisoning with high and low calcium meat diets*

There is a tendency for the guanidine content of the blood to increase slightly several hours after the dose of carbon tetrachloride. This tendency is much exaggerated if meat is eaten. Because of the importance of meat in this respect animals even when on a low calcium diet sometimes escape serious symptoms if they persistently refuse to eat after receiving carbon tetrachloride. From the table it is seen that a rise in guanidine is followed within a few hours by a fall in blood sugar. The difference in the high and low calcium groups on meat diet (A and B) seems to lie in the severity of the subsequent

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The method just described was applied to the study of blood samples taken before and at intervals after the administration of carbon tetrachloride to dogs under various conditions which are known to affect the toxicity of the drug. These figures, together with blood sugar and icteric index determinations on the same samples, are arranged in groups in table 3 and are discussed separately under appropriate headings.

*Carbon tetrachloride poisoning with high and low calcium meat diets*

There is a tendency for the guanidine content of the blood to increase slightly several hours after the dose of carbon tetrachloride. This tendency is much exaggerated if meat is eaten. Because of the importance of meat in this respect animals even when on a low calcium diet sometimes escape serious symptoms if they persistently refuse to eat after receiving carbon tetrachloride. From the table it is seen that a rise in guanidine is followed within a few hours by a fall in blood sugar. The difference in the high and low calcium groups on meat diet (A and B) seems to lie in the severity of the subsequent

TABLE 3—Continued

| Dog number  | Hours after dose | Guanidine | Blood sugar | Icteric index | Remarks                                 |
|---|------------------|-----------|-------------|---------------|---|
| Group B—Dogs on meat—High calcium diet—4 cc CCl <sub>4</sub> per kilogram |                  |           |             |               |   |
| 28-6-7<br>Weight 7.1 kgm.   | Preliminary      | mgm 0.48  | mgm 100     | 0             |   |
|   | 21 hours         | 0.48      | 93          |               | Ate meat + calcium 22 hours after dose  |
|   | 27 hours         | 0.51      | 80          | 1.0           | Good condition                          |
|   | 45 hours         | 0.45      | 92          | 1.0           | Ate meat + Ca salts 46 hours after dose |
|   | 51 hours         | 1.33      | 83          |               | Good condition                          |
|   | 72 hours         | 0.49      | 95          |               | Good condition—recovered                |
|   |                  |           |             |               |   |
| 28-6-8<br>Weight 8.4 kgm.   | Preliminary      | 0.37      | 88          | 0             |   |
|   | 21 hours         | 0.44      | 88          |               | Very quiet—refused to eat               |
|   | 27 hours         | 0.66      | 87          | 9.8           |   |
|   | 45 hours         | 0.55      | 78          | 10.0          | Refused to eat                          |
|   | 72 hours         | 0.89      | 84          | 8.6           | Ate a little meat + calcium             |
|   | 96 hours         | 0.40      | 90          | 2.0           | Recovered                               |
| 28-6-9<br>Weight 8.1 kgm.   | Preliminary      | 0.40      | 95          | 0             |   |
|   | 21 hours         | 0.40      | 80          |               |   |
|   | 27 hours         | 0.96      | 95          | 3.1           | Ate meat + calcium at 22 hours          |
|   | 45 hours         | 0.50      | 87          | 2.5           | Ate meat + calcium at 46 hours          |
|   | 51 hours         | 0.88      | 78          |               |   |
|   | 72 hours         | 0.46      | 84          | Trace         | Well—discharged                         |
| 28-6-10<br>Weight 7.0 kgm.  | Preliminary      | 0.34      | 93          | 0             |   |
|   | 21 hours         | 0.44      | 78          |               | Ate meat at 22 hours                    |
|   | 27 hours         | 0.96      | 64          | 3.5           |   |
|   | 45 hours         | 1.63      | 69          | 2.5           | Refused to eat                          |
|   | 72 hours         | 1.71      | 66          | 10.8          | Very sick                               |
|   | 96 hours         | 0.80      | 70          | 5.0           | Much better                             |
|   | 120 hours        | 0.40      | 80          | 2.0           | Recovered                               |
| 28-2-3<br>Weight 9.9 kgm.   | Preliminary      | 0.47      | 75          |               |   |
|   | 6 hours          | 0.50      | 100         |               | Refused to eat                          |
|   | 24 hours         | 0.66      | 43          |               | Very quiet and sick                     |
|   | 48 hours         | 0.61      | 42          | 10.0          | Ate meat + calcium salts—very quiet     |
|   | 72 hours         | 0.61      | 68          | 12.5          |   |
|   | 102 hours        | 0.30      | 56          |               | Did not eat                             |
|   | 132 hours        | 0.33      | 83          |               | Recovered                               |

TABLE 3—Continued

| Dog number  | Hours after dose | Guanidine   | Blood sugar | Icteric index | Remarks                                 |
|---|------------------|-------------|-------------|---------------|---|
| Group B—Dogs on meat—High calcium diet—4 cc CCl <sub>4</sub> per kilogram |                  |             |             |               |   |
| 28-6-7<br>Weight 7.1 kgm.   | Preliminary      | mgm<br>0.48 | mgm<br>100  | 0             |   |
|   | 21 hours         | 0.48        | 93          |               | Ate meat + calcium 22 hours after dose  |
|   | 27 hours         | 0.51        | 80          | 1.0           | Good condition                          |
|   | 45 hours         | 0.45        | 92          | 1.0           | Ate meat + Ca salts 46 hours after dose |
|   | 51 hours         | 1.33        | 83          |               | Good condition                          |
|   | 72 hours         | 0.49        | 95          |               | Good condition—recovered                |
| 28-6-8<br>Weight 8.4 kgm.   | Preliminary      | 0.37        | 88          | 0             |   |
|   | 21 hours         | 0.44        | 88          |               | Very quiet—refused to eat               |
|   | 27 hours         | 0.66        | 87          | 9.8           |   |
|   | 45 hours         | 0.55        | 78          | 10.0          | Refused to eat                          |
|   | 72 hours         | 0.89        | 84          | 8.6           | Ate a little meat + calcium             |
|   | 96 hours         | 0.40        | 90          | 2.0           | Recovered                               |
| 28-6-9<br>Weight 8.1 kgm.   | Preliminary      | 0.40        | 95          | 0             |   |
|   | 21 hours         | 0.40        | 80          |               |   |
|   | 27 hours         | 0.96        | 95          | 3.1           | Ate meat + calcium at 22 hours          |
|   | 45 hours         | 0.50        | 87          | 2.5           | Ate meat + calcium at 46 hours          |
|   | 51 hours         | 0.88        | 78          |               |   |
|   | 72 hours         | 0.46        | 84          | Trace         | Well—discharged                         |
| 28-6-10<br>Weight 7.0 kgm.  | Preliminary      | 0.34        | 93          | 0             |   |
|   | 21 hours         | 0.44        | 78          |               | Ate meat at 22 hours                    |
|   | 27 hours         | 0.96        | 64          | 3.5           |   |
|   | 45 hours         | 1.63        | 69          | 2.5           | Refused to eat                          |
|   | 72 hours         | 1.71        | 66          | 10.8          | Very sick                               |
|   | 96 hours         | 0.80        | 70          | 5.0           | Much better                             |
|   | 120 hours        | 0.40        | 80          | 2.0           | Recovered                               |
| 28-2-3<br>Weight 9.9 kgm.   | Preliminary      | 0.47        | 75          |               |   |
|   | 6 hours          | 0.50        | 100         |               | Refused to eat                          |
|   | 24 hours         | 0.66        | 43          |               | Very quiet and sick                     |
|   | 48 hours         | 0.61        | 42          | 10.0          | Ate meat + calcium salts—very quiet     |
|   | 72 hours         | 0.61        | 68          | 12.5          |   |
|   | 102 hours        | 0.30        | 56          |               | Did not eat                             |
|   | 132 hours        | 0.33        | 83          |               | Recovered                               |

TABLE 3—*Continued*

| Dog number   | Hours after dose | Guanidine | Blood sugar | Icteric index | Remarks  |
|--|------------------|-----------|-------------|---------------|--|
| Group D—Dogs receiving 4 cc CCl <sub>4</sub> + 4 cc alcohol per kilogram |                  |           |             |               |  |
| 28-4-8   | Preliminary      | 0 34*     | 73          | 0             |  |
| Low calcium meat diet  | 20 hours         | 1 06      | 65          | 11 7          | Ate little meat—vomited it                                 |
| Weight 4 4 kgm   | 25½ hours        | 0 75      | 20          |               | Just dead—died quietly                                     |
| 28-4-9   | Preliminary      | 0 37      | 78          |               |  |
| Low calcium meat diet  | 20 hours         | 0 42      | 51          |               | Tetanic convulsions  |
| Weight 4 3 kgm   | 33 hours         | 0 66      | 20          |               | Tetanic convulsions and death                              |
| 28-4-11  | Preliminary      | 0 46      | 78          | 0             |  |
| Low calcium meat diet  | 20 hours         | 1 23      | 78          |               | Ate meat at 21 hours                                       |
| Weight 5 6 kgm.  | 43 hours         | 1 61      | 50          | 15 9          | Tremors noted<br>In coma—died few minutes later            |
| 28-4-12  | Preliminary      | 0 48†     | 71          | 0             |  |
| Low calcium meat diet  | 20 hours         | 0 80      | 62          | 4 9           | Ate meat at 21 hours                                       |
| Weight 4 8 kgm   | 26 hours         | 1 60      | 54          |               | Quite sick—quiet   |
|  | 34 hours         | 0 83      | 48          |               | Very sick—barely conscious—died 2-3 hours—later            |
| 28-2-20  | Preliminary      | 0 48      | 86          | 0             |  |
| Mixed diet High calcium  | 4 hours          | 0 46      | 79          |               | Ate meat at 5 hours  |
| Weight 10 9 kgm  | 7 hours          | 0 76      | 68          |               |  |
|  | 11 hours         | 1 20      | 43          |               | Muscle twitching   |
|  | 24 hours         | 1 26      | 25          |               | Very sick—lying on side—muscle twitching                   |
|  | 30 hours         | 0 87      | 23          | 9 3           | Violent tetanic convulsions—died shortly after last sample |

\* The corresponding creatine concentrations for this and the following blood samples of this animal are 3 11, 2 39, and 2 43 mgm per 100 cc of blood respectively

† The corresponding creatine concentrations for this and the following blood samples of this animal are 3 00, 1 25, 1 20 and 1 00 mgm per 100 cc. of blood respectively

TABLE 3—Continued

| Dog number   | Hours after dose | Guanidine | Blood sugar | Icteric index | Remarks  |
|--|------------------|-----------|-------------|---------------|--|
| Group D—Dogs receiving 4 cc CCl <sub>4</sub> + 4 cc alcohol per kilogram |                  |           |             |               |  |
| 28-4-8   | Preliminary      | 0 34*     | 73          | 0             |  |
| Low calcium meat diet  | 20 hours         | 1 06      | 65          | 11 7          | Ate little meat—vomited it                                 |
| Weight 4 4 kgm   | 25½ hours        | 0 75      | 20          |               | Just dead—died quietly                                     |
| 28-4-9   | Preliminary      | 0 37      | 78          |               |  |
| Low calcium meat diet  | 20 hours         | 0 42      | 51          |               | Tetanic convulsions  |
| Weight 4 3 kgm   | 33 hours         | 0 66      | 20          |               | Tetanic convulsions and death                              |
| 28-4-11  | Preliminary      | 0 46      | 78          | 0             |  |
| Low calcium meat diet  | 20 hours         | 1 23      | 78          |               | Ate meat at 21 hours<br>Tremors noted                      |
| Weight 5 6 kgm.  | 43 hours         | 1 61      | 50          | 15 9          | In coma—died few minutes later                             |
| 28-4-12  | Preliminary      | 0 48†     | 71          | 0             |  |
| Low calcium meat diet  | 20 hours         | 0 80      | 62          | 4 9           | Ate meat at 21 hours                                       |
| Weight 4 8 kgm   | 26 hours         | 1 60      | 54          |               | Quite sick—quiet   |
|  | 34 hours         | 0 83      | 48          |               | Very sick—barely conscious—died 2-3 hours—later            |
| 28-2-20  | Preliminary      | 0 48      | 86          | 0             |  |
| Mixed diet High calcium  | 4 hours          | 0 46      | 79          |               | Ate meat at 5 hours  |
| Weight 10 9 kgm  | 7 hours          | 0 76      | 68          |               |  |
|  | 11 hours         | 1 20      | 43          |               | Muscle twitching   |
|  | 24 hours         | 1 26      | 25          |               | Very sick—lying on side—muscle twitching                   |
|  | 30 hours         | 0 87      | 23          | 9 3           | Violent tetanic convulsions—died shortly after last sample |

\* The corresponding creatine concentrations for this and the following blood samples of this animal are 3 11, 2 39, and 2 43 mgm per 100 cc of blood respectively

† The corresponding creatine concentrations for this and the following blood samples of this animal are 3 00, 1 25, 1 20 and 1 00 mgm per 100 cc. of blood respectively



TABLE 3—Continued

| Dog number   | Hours after dose | Guanidine | Blood sugar | Icteric index | Remarks  |
|--|------------------|-----------|-------------|---------------|--|
| Group F—Experimental guanidine poisoning—Continued     |                  |           |             |               |  |
| 28-7-10  | Preliminary      | mgm 0 40  | mgm 80      | 0             |  |
| Low calcium meat diet                                  | 4 hours          | 3 84      | 62          |               | Restless, nausea, fibrillary twitching of muscles        |
| Weight 8 1 kgm   | 6 hours          | 3 68      | 51          |               | Extensor spasms when handled                             |
| 200 mgm guanidine hydrochloride per kgm subcutaneously | 8 hours          | 2 22      | 42          |               | Quiet unless handled, then convulsions                   |
|  | 11 hours         | 1 50      | 37          | 0             | Bloody diarrhea—quiet—unconscious Died few minutes later |

hypoglycemia rather than in the concentrations of guanidine reached. Further evidence that calcium is responsible for the avoidance of dangerously low blood sugar levels in the animals in Group B is furnished by later experiments (see chart A) in which rapidly falling blood sugar concentrations are maintained above the danger level by the administration of calcium salts. One of the few exceptions to the usual rule of low resistance to intoxication in low calcium animals is represented in the second member of Group A. In spite of low calcium intake and the production of a high guanidine concentration in the blood a safe blood sugar level is maintained. The low icteric index too is like those seen in animals on high calcium diet. In the other direction an occasional animal on high calcium diet will succumb with the same symptoms and blood changes shown by animals on deficient calcium diet. We have been unable to avoid a few such discrepancies in each group. However, when a condition is being studied in which nitrogen, sugar, and calcium metabolisms seem all to be involved this is perhaps not to be wondered at. Feeding calcium cannot guarantee its absorption and utilization, nor can dogs with varying previous life histories all be brought to comparable degrees of calcium lack by 2 or 3 weeks of special diet.

*Carbon tetrachloride poisoning with bread and milk diet.* To avoid the rise in guanidine produced by eating meat 10 animals were run on bread and milk diet and all gave consistent results. Three typical

TABLE 3—*Continued*

| Dog number   | Hours after dose | Guanidine | Blood sugar | Icteric index | Remarks  |
|--|------------------|-----------|-------------|---------------|--|
| Group F—Experimental guanidine poisoning—Continued     |                  |           |             |               |  |
| 28-7-10  | Preliminary      | 0 40      | 80          | 0             |  |
| Low calcium meat diet                                  | 4 hours          | 3 84      | 62          |               | Restless, nausea, fibrillary twitching of muscles        |
| Weight 8.1 kgm   | 6 hours          | 3 68      | 51          |               | Extensor spasms when handled                             |
| 200 mgm guanidine hydrochloride per kgm subcutaneously | 8 hours          | 2 22      | 42          |               | Quiet unless handled, then convulsions                   |
|  | 11 hours         | 1 50      | 37          | 0             | Bloody diarrhea—quiet—unconscious Died few minutes later |

hypoglycemia rather than in the concentrations of guanidine reached. Further evidence that calcium is responsible for the avoidance of dangerously low blood sugar levels in the animals in Group B is furnished by later experiments (see chart A) in which rapidly falling blood sugar concentrations are maintained above the danger level by the administration of calcium salts. One of the few exceptions to the usual rule of low resistance to intoxication in low calcium animals is represented in the second member of Group A. In spite of low calcium intake and the production of a high guanidine concentration in the blood a safe blood sugar level is maintained. The low icteric index too is like those seen in animals on high calcium diet. In the other direction an occasional animal on high calcium diet will succumb with the same symptoms and blood changes shown by animals on deficient calcium diet. We have been unable to avoid a few such discrepancies in each group. However, when a condition is being studied in which nitrogen, sugar, and calcium metabolisms seem all to be involved this is perhaps not to be wondered at. Feeding calcium cannot guarantee its absorption and utilization, nor can dogs with varying previous life histories all be brought to comparable degrees of calcium lack by 2 or 3 weeks of special diet.

*Carbon tetrachloride poisoning with bread and milk diet.* To avoid the rise in guanidine produced by eating meat 10 animals were run on bread and milk diet and all gave consistent results. Three typical

chloride which produce similar symptoms do so by producing comparable concentrations of guanidine in the blood. To demonstrate this 12 cases of guanidine poisoning have been studied and the concentrations of guanidine in the blood determined. All cases gave similar results and three are included in Table 3 as Group F. Our figures are in close agreement with those reported by Major, Orr and Weber (38). Although the values range somewhat higher than those usually reached in carbon tetrachloride poisoning they are still of the same general order of magnitude. It must also be remembered that in carbon tetrachloride and chloroform poisoning the depression of ionized calcium due to the retention of bile pigments would tend to increase the effect of a given concentration of guanidine above that produced in a normal animal.

*The effect of calcium on the hypoglycemias seen in carbon tetrachloride intoxication and guanidine poisoning*

Looking back to the protocols describing the prompt relief following the administration of calcium salts to dogs with severe carbon tetrachloride intoxication, it seems probable that a large factor in the cures must have been a restoration to normal of the very low blood sugar levels. Underhill and Blatherwick (39) (40) have shown that the hypoglycemia after parathyroidectomy can be relieved by calcium administration. Watanabe (24) was, however, unable to influence the low blood sugar levels produced by guanidine administration by the subcutaneous administration of calcium lactate. We believe that this failure was due to inadequate calcium therapy. The subcutaneous administration of calcium lactate is a very slow way of furnishing calcium ions to cases of such acute need as is seen in guanidine poisoning. We have found that calcium chloride administered intravenously will usually restore the blood sugar to normal in either carbon tetrachloride or guanidine poisoning. Even the administration of calcium chloride by mouth often suffices to check a rapidly falling blood sugar in animals in carbon tetrachloride poisoning. Such a restoration is not accomplished by reducing the guanidine concentration because a return to normal blood sugar can be brought about during a period when the guanidine concentration in the blood is steadily rising. This point as well as the prompt elevation of blood

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Sometimes after prolonged and very severe intoxication produced either by guanidine or carbon tetrachloride, death occurs in spite of intravenous administration of calcium chloride. We hope in later work to show that these failures occur when there has been a depletion

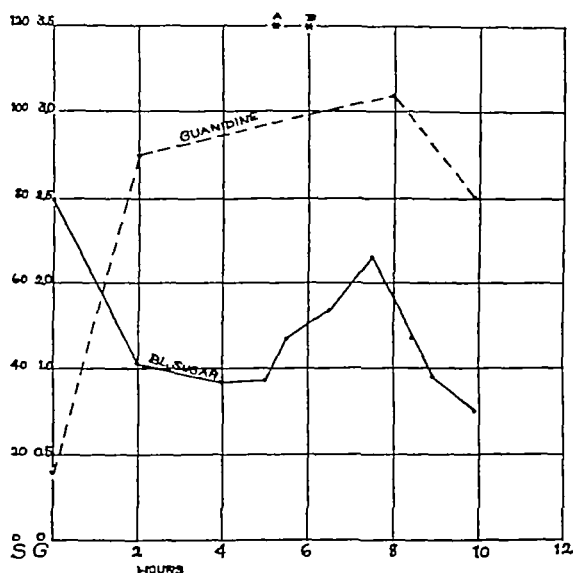


CHART B EFFECT OF CALCIUM ADMINISTRATION ON BLOOD SUGAR CONCENTRATION IN EXPERIMENTAL GUANIDINE POISONING

The figures for blood sugar (S) and guanidine (G) are in terms of milligrams per 100 cc of blood

Dog no 28-6-19 On low calcium meat diet for 2 to 3 weeks before receiving 200 mgm guanidine hydrochloride per kilogram subcutaneously. Typical severe intoxication developed after the administration of the dose

\*A, 500 mgm  $\text{CaCl}_2$  given intravenously as 10 per cent solution, \*B, 300 mgm  $\text{CaCl}_2$  given intravenously as 10 per cent solution

The symptoms were much relieved during the time that the blood sugar was elevated. After medication was withheld the dog grew rapidly worse, convulsions reappeared, and death occurred 10 hours after the dose with a blood sugar concentration of 30 mgm per 100 cc blood

of all the glycogen from the liver. Under these conditions calcium chloride can hardly be expected to furnish the needed sugar. The method by which in the successful cases blood sugar is increased after calcium is furnished is at present unknown. The return of blood

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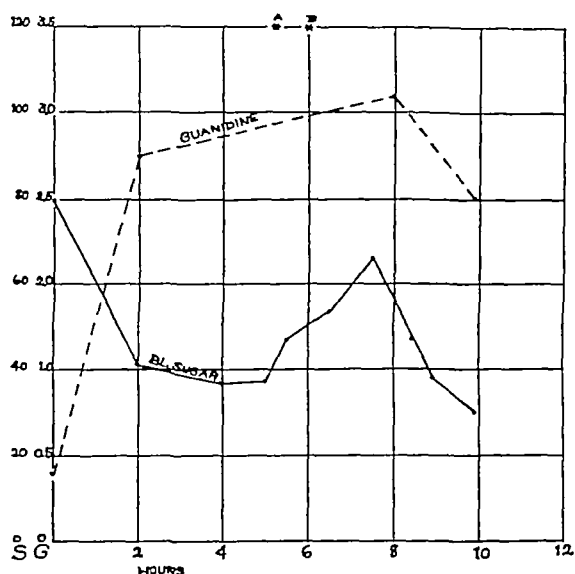


CHART B EFFECT OF CALCIUM ADMINISTRATION ON BLOOD SUGAR CONCENTRATION IN EXPERIMENTAL GUANIDINE POISONING

The figures for blood sugar (S) and guanidine (G) are in terms of milligrams per 100 cc of blood

Dog no 28-6-19 On low calcium meat diet for 2 to 3 weeks before receiving 200 mgm guanidine hydrochloride per kilogram subcutaneously. Typical severe intoxication developed after the administration of the dose

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functional studies already under way will be able to answer the question as to whether these glands have been damaged by the drugs which we know bring about a retention of guanidine. Whatever the normal disposal of guanidine is, it seems to be a very effective one because relatively enormous doses of guanidine must be administered to a normal dog to produce a concentration of 2 to 3 mgm of guanidine per 100 cc of blood. At present we can only state that both carbon tetrachloride and chloroform cause a serious interference with this mechanism and a retention of guanidine results. The toxic symptoms produced by this retained guanidine are very similar to those seen in experimental guanidine poisoning. The outstanding features of both intoxications are gastro-intestinal irritation, nervous hyperexcitability followed by depression, extreme hypoglycemia, and death. In both conditions calcium has a highly favorable action. In carbon tetrachloride poisoning the need for calcium is rendered doubly acute by the increased guanidine and the simultaneous depletion of calcium ions by a retention of bile pigments. When this need is met by furnishing calcium most cases of intoxication can be prevented or cured.

Practical suggestions regarding the management of a case to be treated with carbon tetrachloride would emphasize first of all the importance of a liberal amount of calcium in the preliminary diet. In order to avoid the tendency toward increased guanidine in the blood meat should be avoided and a diet rich in calcium and carbohydrate substituted. A bread and milk diet is an easy method of furnishing both calcium and carbohydrate in adequate amounts. With these precautions cases of intoxication should be extremely rare. If poisoning should occur, a combination of calcium chloride and dextrose therapy seems indicated and in our experience has nearly always proved effective.

#### SUMMARY AND CONCLUSIONS

- 1 Carbon tetrachloride produces a severe intoxication in dogs on a meat diet which is low in calcium while the addition of calcium salts to the meat diet, or the feeding of a liberal mixed diet without meat causes a high degree of tolerance to the drug. Furthermore, cases of poisoning can usually be cured by calcium therapy.

- 2 The outstanding features of the intoxication are gastro-intestinal

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- 2 The outstanding features of the intoxication are gastro-intestinal



This investigation is one of a series of studies being made under the direction of Dr P D Lamson on the pharmacology and toxicology of carbon tetrachloride. The work is being carried on with the support of the International Health Board.

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This investigation is one of a series of studies being made under the direction of Dr P D Lamson on the pharmacology and toxicology of carbon tetrachloride. The work is being carried on with the support of the International Health Board.

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#### PROCEDURE

In the carrying out of this investigation, two tests for the presence of duodenal contents in the stomach were used, the appearance of bile and the presence of tryptic activity

Twenty-three examinations were made on cases as follows

- 1-10—total achylia, giving no acid on fractional meals or after injection of histamine (pernicious anemia)
- 11-14—duodenal ulcer
- 15—retroperitoneal tumor
- 16—asthma
- 17—compression myelitis
- 18—normal
- 19-20—simple achylia
- 21—pyloric obstruction
- 22—gastroenterostomy

In carrying out the experiments, the contents of the fasting stomach were removed through a Rehfuess tube with the olive located in the lower part of the stomach. The stomach was then washed at 3- to 5-minute intervals with small amounts of water or of the reagent selected, and samples immediately withdrawn, or the reagent was allowed to remain in the stomach and portions fractioned out at 5- to 10-minute intervals. The samples obtained were examined for bile, and tested for the presence of trypsin.

#### *Test for trypsin*

*Principle* The samples of gastric content are mixed with purified egg albumin, incubated for 48 hours at 37°, when the digestion mixture is tested quantitatively for free amino groups

*Procedure* About 15 cc of each sample of gastric content are shaken with permutit to remove ammonia and filtered or centrifuged. A few cubic centimeters of the clear liquid obtained should be tested with Nessler's reagent to determine if the ammonia has been completely removed. If not, it should be shaken again with permutit and refiltered.

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in a graduated test tube in as small an amount as possible of 10 per cent NaOH and water added to make up the desired volume

## EXPERIMENTS

The first 10 experiments were on cases of pernicious anemia. The first of these is represented in figure 1. The fasting contents were removed and the stomach washed 10 times with 250 cc of water at 37° and completely emptied after each washing. Another 250 cc were

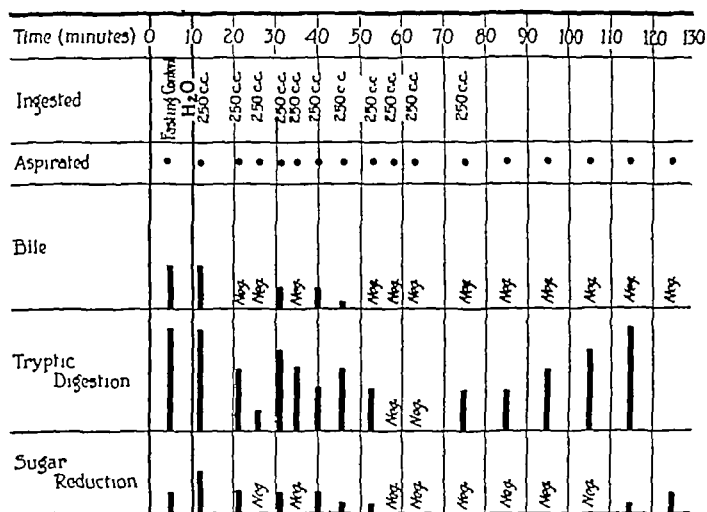


FIG 1 (EXPERIMENT 1) SHOWS THE PRESENCE IN THE STOMACH OF TRYPSIN DURING REPEATED WASHINGS WITH WATER, EVEN IN THE ABSENCE OF BILE

Note the increase in trypsin as the stomach empties

Subject Wm F Diagnosis Pernicious anemia Date January 22, 1927

then introduced and samples removed at once and after 10 minute intervals for fifty minutes. Three tests were employed for duodenal regurgitation,—the presence of bile, tryptic activity, and the inversion of sucrose. The last names was tested for by incubating a few cubic centimeters of each sample with a solution of cane sugar and the solution tested, after four hours, with Benedict's reagent for reducing substances.

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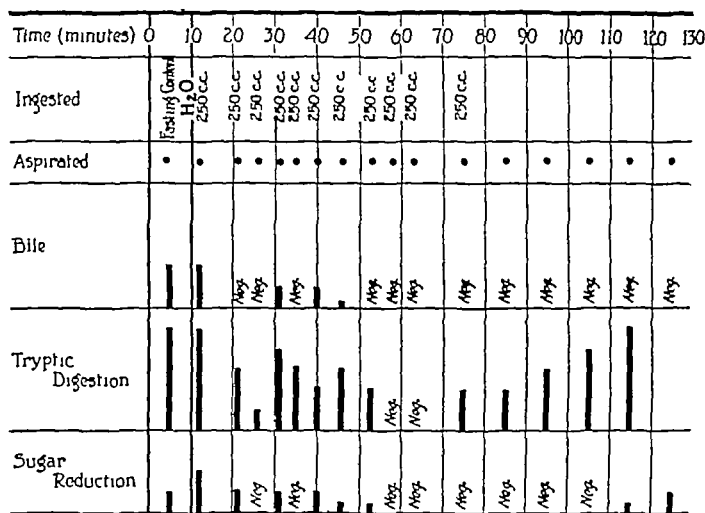


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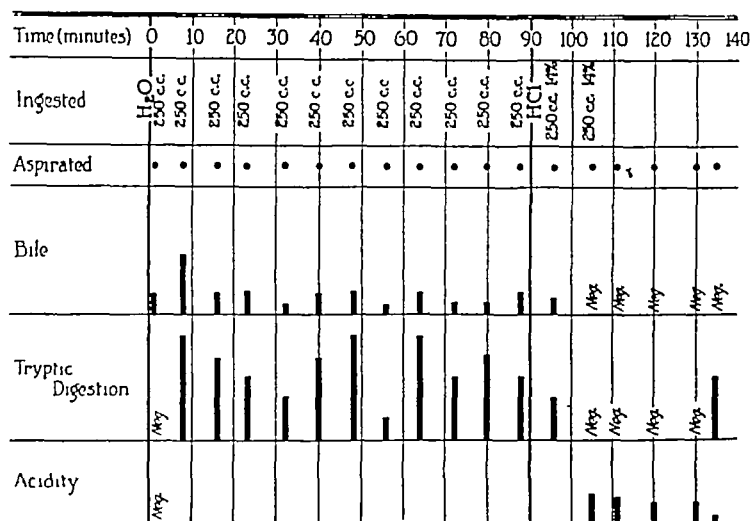


FIG 4 (EXPERIMENT 4) SHOWS THE CONTINUOUS PRESENCE IN THE STOMACH OF BILE AND TRYPSIN DURING WASHINGS WITH WATER, THE ABSENCE OF BOTH WITH DILUTE ACID

Subject Wm F Diagnosis Pernicious anemia Date January 27, 1927

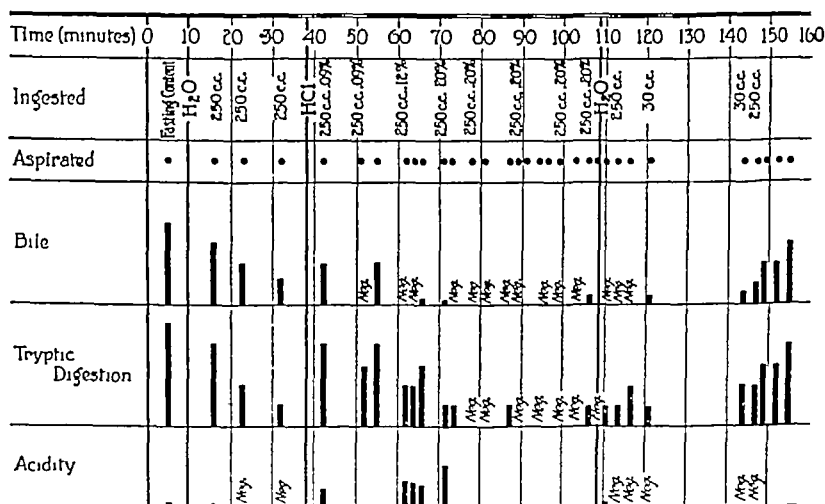


FIG 5 (EXPERIMENT 5) SHOWS THE PRESENCE IN THE STOMACH OF BILE AND TRYPSIN DURING WASHINGS WITH WATER AND DILUTE ACID, THEIR COMPLETE DISAPPEARANCE DURING WASHINGS WITH MORE CONCENTRATED ACID

Subject Wm F Diagnosis Pernicious anemia Date February 5, 1927

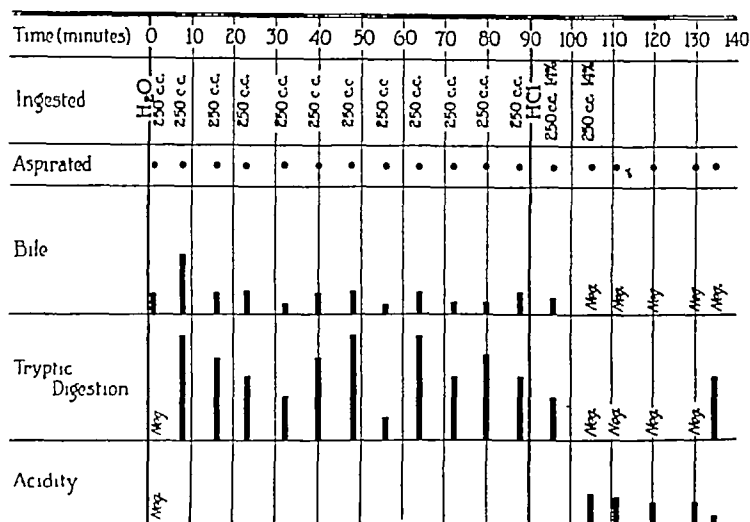


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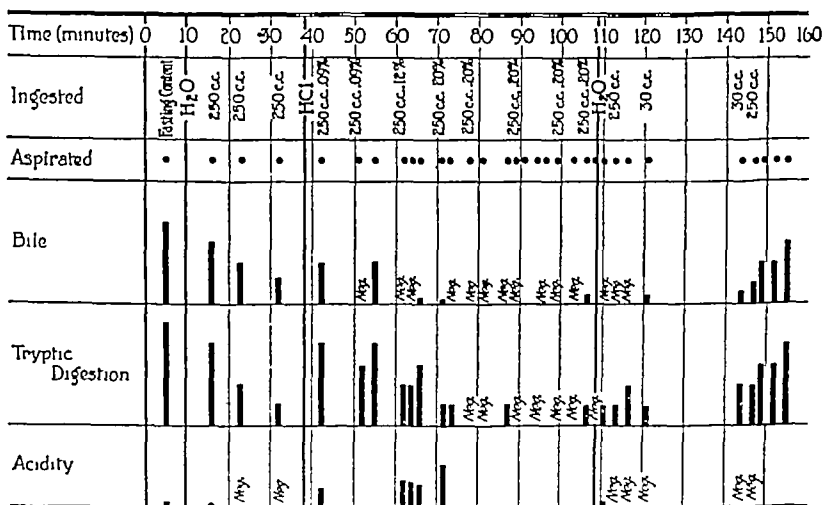


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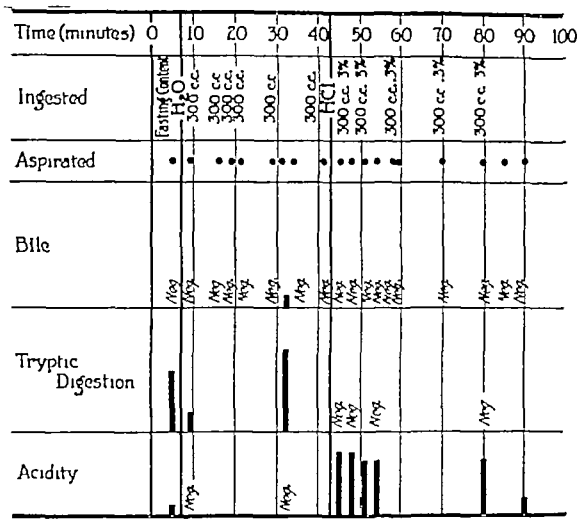


FIG 6 (EXPERIMENT 6) SHOWS THE PRESENCE IN THE STOMACH OF TRYPSIN DURING WASHINGS WITH WATER, ITS DISAPPEARANCE DURING WASHINGS WITH 0.3 PER CENT ACID

Subject Wm W    Diagnosis Pernicious anemia    Date March 3, 1927

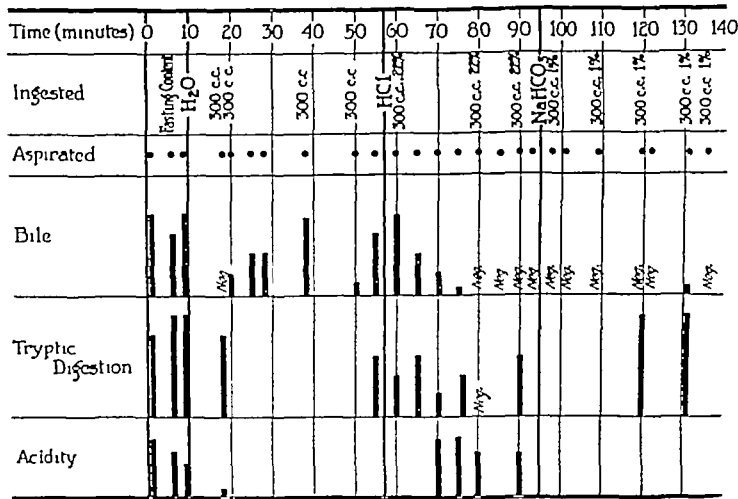


FIG 7 (EXPERIMENT 11) SHOWS THE DECREASE OF BILE IN THE STOMACH DURING WASHINGS WITH ACID, TRYPSIN REMAINING UNCHANGED, RETURN OF BILE AND A MARKED INCREASE OF TRYPSIN ON WASHINGS WITH ALKALI

Subject Axel J    Diagnosis Duodenal ulcer    Date March 3, 1927

DUODENAL REGURGITATION

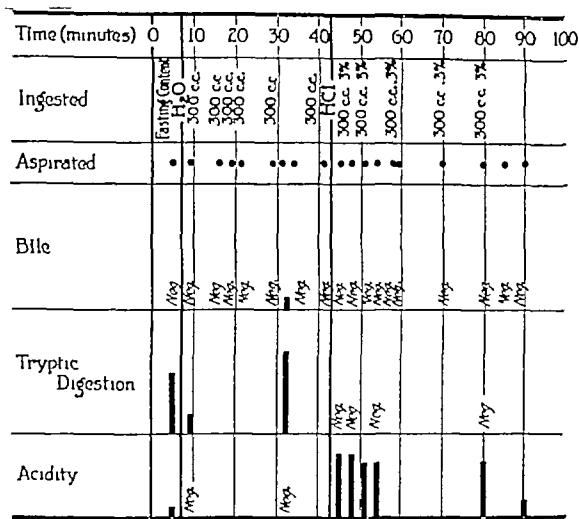


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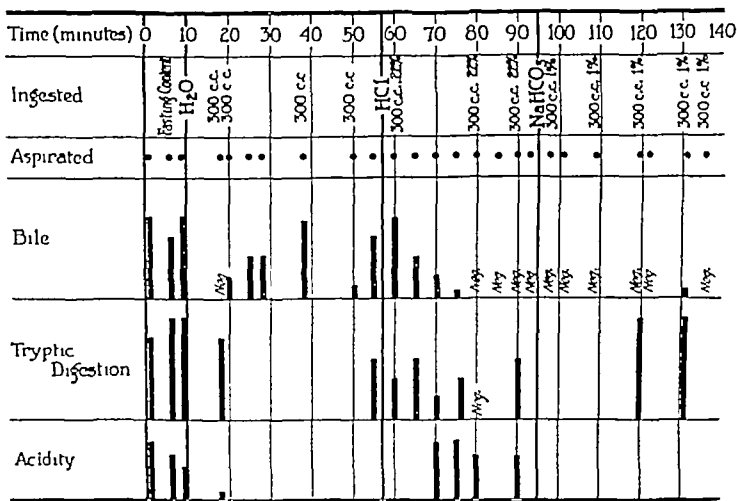


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(0.3 per cent HCl) and where tryptic activity was lacking entirely during the entire period of acid washing. Bile was positive only once, in one of the samples of washing with water.

The results of these cases together with four others, nos. 7 to 10, are tabulated in table 1. In column 1 are recorded the numbers of the cases. In column 2 are shown the appearance or non-appearance of bile and trypsin in the fasting contents, and in the next five columns the numbers of washings with water and with solutions of HCl, together

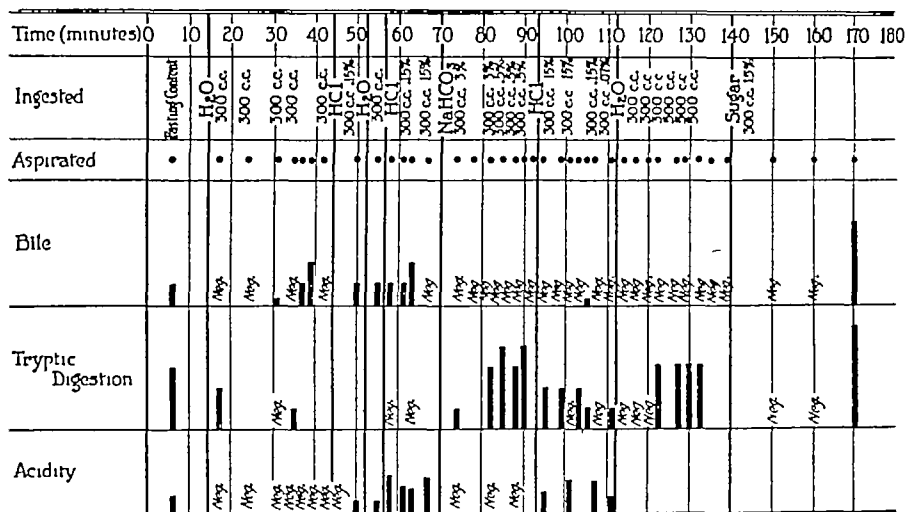


FIG. 8 (EXPERIMENT 15) SHOWS THE INDEPENDENT APPEARANCE IN THE STOMACH OF BILE AND TRYPSIN

Subject Wm. C. Diagnosis: Retroperitoneal tumor. Date: February 17, 1927.

with the frequency of the appearance of bile and trypsin in the aspirated samples.

Case 11 (fig. 7 and table 2) was diagnosed as one of duodenal ulcer. Tryptic digestion was present during the entire time except in one acid washing but was somewhat decreased during the entire period of acid ingestion. Bile disappeared during the same period and failed to reappear except in traces after 30 minutes of washing with NaHCO<sub>3</sub>. The other cases (nos. 12 to 19), the findings from which are also tabulated in table 2, are of miscellaneous diagnoses other than pernicious anemia.

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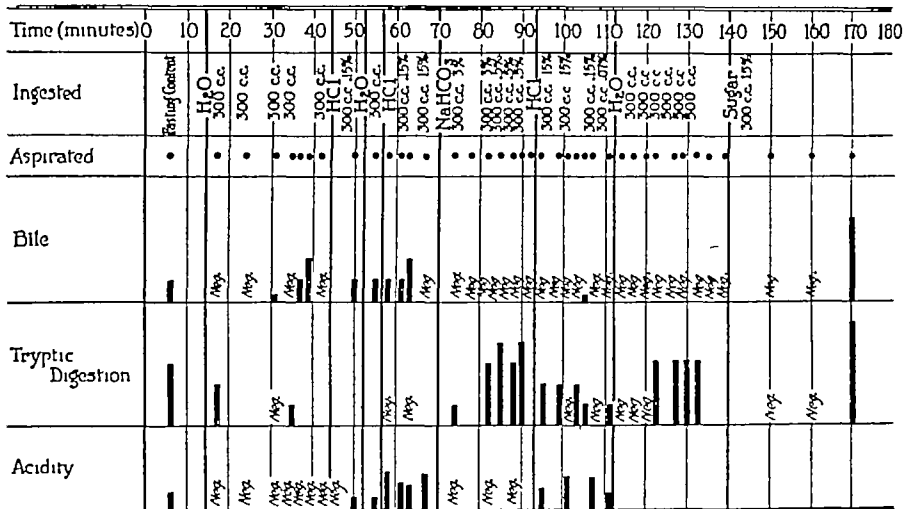


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the gallbladder and the pancreas always flow at the same time, and it seems quite reasonable to assume that one might get gushes of bile containing very little or no pancreatic secretion. Further, Baldwin found that an accessory pancreatic duct (fig 10), the duct of Santorini, which opens about three-fourths inch, to one inch, higher up than the common bile duct, was patent to injection in 77 per cent of the cases and patent to dissection in over 85 per cent of the cases that he examined. He found also that in some cases this accessory duct was large and apparently performed most of the work, in others it was smaller and sometimes was entirely functionless. It seems reasonable to suppose that pancreatic juice might flow to a varying extent through this duct even when the common duct is not functioning and when no bile is getting into the duodenum, and in the cases pictured by Baird, Campbell and Hearn, where a duodenal tube was placed at the level of the ampulla, and the bile removed by continuous aspiration, it may be that bile-free duodenal contents containing pancreatic juice was secreted into the duodenum through the accessory duct and was regurgitated into the stomach.

## *2 Factors affecting the frequency of regurgitation*

*a Water* In tables 3 and 4 are listed the same experiments, together with the number of times regurgitation was observed, as judged by the presence of either bile or trypsin, and the number of times that regurgitation did not occur, as concluded from the fact that both tests were negative.

As has been brought out in the preceding paragraphs, regurgitation had occurred in all the fasting contents examined. In the washings which followed, regurgitation was found most frequently with the use of water, about the same number of times with sodium bicarbonate, and with decreasing frequency under the influence of acids of increasingly greater concentrations. This evidently is not in harmony with Boldyreff.

Previous workers have called attention to the frequency of regurgitation when water is used as a test meal. Rosemann (1907), for instance, in preparing animals with gastric fistulae for sham feeding, states, "Einmal gewann ich den Eindruck, als ob unter dem Einfluss dieser Spülung (mit destilliertem wasser), besonders leicht ein Zurück-

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On the basis of these and other similar observations Boldyreff (1911) elaborated a definite theory of duodenal regurgitation. He states that

TABLE 4

*Regurgitation in miscellaneous cases. Shows the number of aspirations tested for both bil. and trypsin, the number positive for one (indicating regurgitation) and the number negative for both (indicating no regurgitation)*

| Experiment number | Fasting contents | H <sub>2</sub> O      |          |          | NaHCO <sub>3</sub> 1 per cent |          |          | HCl, 0.14 per cent    |          |          | HCl, 0.2 per cent     |          |          | HCl 0.3 per cent      |          |          |                       |  |
|-------------------|------------------|-----------------------|----------|----------|-------------------------------|----------|----------|-----------------------|----------|----------|-----------------------|----------|----------|-----------------------|----------|----------|-----------------------|--|
|                   |                  | Total number of tests | Number + | Number - | Total number of tests         | Number + | Number - | Total number of tests | Number + | Number - | Total number of tests | Number + | Number - | Total number of tests | Number + | Number - |                       |  |
|                   |                  |                       |          |          |                               |          |          |                       |          |          |                       |          |          |                       |          |          |                       |  |
| 11                | +                | 2                     | 2        | 0        | 2                             | 2        | 0        |                       |          |          | 6                     | 5        | 1        |                       |          |          | Duodenal ulcer        |  |
| 12                | +                | 7                     | 5        | 2        | 6                             | 5        | 1        |                       |          |          |                       |          |          | 3                     | 1        | 2        | Duodenal ulcer        |  |
| 13                | +                | 5                     | 5        | 0        | 4                             | 4        | 0        |                       |          |          |                       |          |          | 2                     | 0        | 2        | Duodenal ulcer        |  |
| 14                | +                | 2                     | 2        | 0        |                               |          |          |                       |          |          |                       |          |          | 6                     | 3        | 3        | Duodenal ulcer        |  |
| 15                | +                | 10                    | 7        | 3        | 5                             | 5        | 0        | 9                     | 5        | 4        |                       |          |          |                       |          |          | Retroperitoneal tumor |  |
| 16                | +                | 6                     | 4        | 2        |                               |          |          |                       |          |          |                       |          |          | 2                     | 0        | 2        | Asthma                |  |
| 17                | +                | 2                     | 1        | 1        | 3                             | 2        | 1        |                       |          |          |                       |          |          | 5                     | 2        | 3        | Compression myelitis  |  |
| 18                | +                | 3                     | 2        | 1        | 5                             | 0        | 5        | 2                     | 2        | 0        |                       |          |          |                       |          |          | Normal                |  |
| 19                | +                | 6                     | 4        | 2        | 2                             | 1        | 1        |                       |          |          |                       |          |          | 5                     | 1        | 4        | Simple achylia        |  |
| Total             |                  | 9                     | 43       | 32       | 11                            | 27       | 19       | 8                     | 11       | 7        | 4                     | 6        | 5        | 1                     | 23       | 7        | 16                    |  |
| Per cent of total |                  | 100                   |          |          |                               |          |          |                       |          |          |                       |          |          |                       |          |          |                       |  |
|                   |                  |                       | 74       | 26       |                               | 70       | 30       |                       | 64       | 36       |                       | 83       | 17       |                       | 30       | 70       |                       |  |
| 23                | *                | 9                     | 9        | 0        | 4                             | 4        | 0        |                       |          |          |                       |          |          | 6                     | 6        | 0        | Polya's operation     |  |
| Per cent of total |                  |                       |          |          |                               |          |          |                       |          |          |                       |          |          |                       |          |          |                       |  |
|                   |                  |                       | 100      | 0        |                               | 100      | 0        |                       |          |          |                       |          |          |                       | 100      | 0        |                       |  |

\* Not tested

when the gastric content is too acid, or the acid is present in the stomach in too large amounts, the alkaline intestinal juice (especially the pancreatic juice) comes in and neutralizes it. The same thing may happen when no acid is introduced, but only gastric juice is present, since the juice as secreted has a much higher acidity (0.5 per cent HCl)

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| Experiment number | Fasting contents | H <sub>2</sub> O      |          |          | NaHCO <sub>3</sub> 1 per cent |          |          | HCl, 0.14 per cent    |          |          | HCl, 0.2 per cent     |          |          | HCl 0.3 per cent      |          |          |                       |  |
|-------------------|------------------|-----------------------|----------|----------|-------------------------------|----------|----------|-----------------------|----------|----------|-----------------------|----------|----------|-----------------------|----------|----------|-----------------------|--|
|                   |                  | Total number of tests | Number + | Number - | Total number of tests         | Number + | Number - | Total number of tests | Number + | Number - | Total number of tests | Number + | Number - | Total number of tests | Number + | Number - |                       |  |
| 11                | +                | 2                     | 2        | 0        | 2                             | 2        | 0        |                       |          |          | 6                     | 5        | 1        |                       |          |          | Duodenal ulcer        |  |
| 12                | +                | 7                     | 5        | 2        | 6                             | 5        | 1        |                       |          |          |                       |          |          | 3                     | 1        | 2        | Duodenal ulcer        |  |
| 13                | +                | 5                     | 5        | 0        | 4                             | 4        | 0        |                       |          |          |                       |          |          | 2                     | 0        | 2        | Duodenal ulcer        |  |
| 14                | +                | 2                     | 2        | 0        |                               |          |          |                       |          |          |                       |          |          | 6                     | 3        | 3        | Duodenal ulcer        |  |
| 15                | +                | 10                    | 7        | 3        | 5                             | 5        | 0        | 9                     | 5        | 4        |                       |          |          |                       |          |          | Retroperitoneal tumor |  |
| 16                | +                | 6                     | 4        | 2        |                               |          |          |                       |          |          |                       |          |          | 2                     | 0        | 2        | Asthma                |  |
| 17                | +                | 2                     | 1        | 1        | 3                             | 2        | 1        |                       |          |          |                       |          |          | 5                     | 2        | 3        | Compression myelitis  |  |
| 18                | +                | 3                     | 2        | 1        | 5                             | 0        | 5        | 2                     | 2        | 0        |                       |          |          |                       |          |          | Normal                |  |
| 19                | +                | 6                     | 4        | 2        | 2                             | 1        | 1        |                       |          |          |                       |          |          | 5                     | 1        | 4        | Simple achylia        |  |
| Total             |                  | 9                     | 43       | 32       | 11                            | 27       | 19       | 8                     | 11       | 7        | 4                     | 6        | 5        | 1                     | 23       | 7        | 16                    |  |
| Per cent of total |                  | 100                   |          | 74       | 26                            |          | 70       | 30                    |          | 64       | 36                    |          | 83       | 17                    |          | 30       | 70                    |  |
| 23                | *                | 9                     | 9        | 0        | 4                             | 4        | 0        |                       |          |          |                       |          |          | 6                     | 6        | 0        | Polya's operation     |  |
| Per cent of total |                  |                       | 100      | 0        |                               | 100      | 0        |                       |          |          |                       |          |          |                       | 100      | 0        |                       |  |

\* Not tested

when the gastric content is too acid, or the acid is present in the stomach in too large amounts, the alkaline intestinal juice (especially the pancreatic juice) comes in and neutralizes it. The same thing may happen when no acid is introduced, but only gastric juice is present, since the juice as secreted has a much higher acidity (0.5 per cent HCl)

and doubtful in 4. According to these figures, regurgitation sometimes accompanies high acidity and sometimes is lacking. On the other hand, it may be present or absent in cases of achlorhydria.

Hicks and Vischer (1915) got regurgitation in 6 out of 30 trials when 150 cc 0.5 per cent HCl was left in a dog's stomach for 15 minutes and in 15 out of 36 trials when left for 30 minutes. When 100 cc of acid of lower concentration, i. e., 0.4 per cent HCl, was left in the stomach for 20 minutes, no regurgitation occurred in 100 per cent of 10 cases.

In our own experiments we did not obtain conclusive results from the use of acid as concentrated as 0.5 per cent HCl, as the patients usually either vomited or felt definite symptoms of gagging, which was invariably accompanied by the passage of bile and pancreatic juice in large amounts through the pylorus. We therefore used 0.3 per cent HCl in most of our cases and found that unless large amounts were introduced, gagging seldom occurred. In the pernicious anemia cases, the tolerance to acids was especially low, and in one instance even 0.09 per cent HCl could not be used.

As stated above, regurgitation occurred less frequently when acid was introduced, than when water or alkali. In the pernicious anemia cases (table 3), regurgitation occurred in 100 per cent of the fasting contents, in 92 per cent of the water washings, 91 per cent of the 0.09 per cent HCl samples, and 62 per cent, 44 per cent and 31 per cent with 0.14 per cent, 0.2 per cent and 0.3 per cent HCl solutions respectively. The records for the miscellaneous cases (table 4) are not dissimilar, except that the frequency of regurgitation in the presence of water is somewhat less, (74 per cent), indicating that the atonic sphincter of pernicious anemia reacts to the slight stimulus of water less readily than does the normal.

The discrepancy between our results and Morse's may possibly be explained in another way. As will be recalled, he found greater regurgitation with higher concentrations of acids. Morse examined his aspirated solutions for bile but not for pancreatic juice. He judged regurgitation in the absence of bile solely by measuring the relative amounts of gastric content recovered after one-half hour. He apparently does not consider the different rates at which water and acids are normally discharged from the stomach. It has been shown by Ivy (1918) that water in both man and dogs begins to leave the stom-

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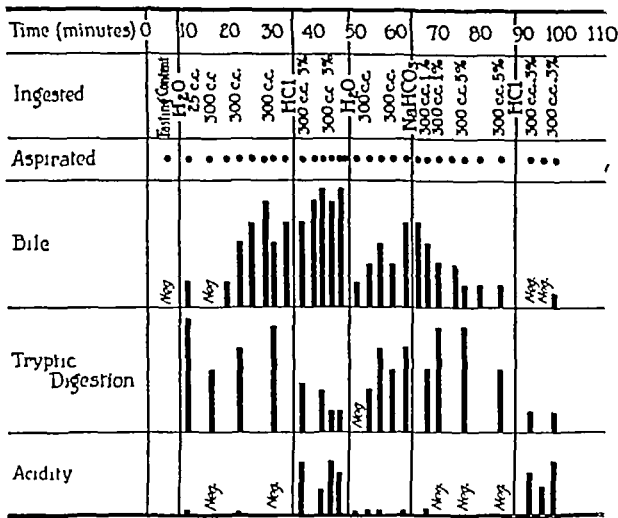


FIG 9 (EXPERIMENT 23 ) SHOWS THE CONSTANT PRESENCE IN THE STOMACH OF DUODENAL CONTENT AFTER GASTROENTEROSTOMY

Subject Chas C Diagnosis Polya's operation for pyloric carcinoma  
Date April 16, 1927

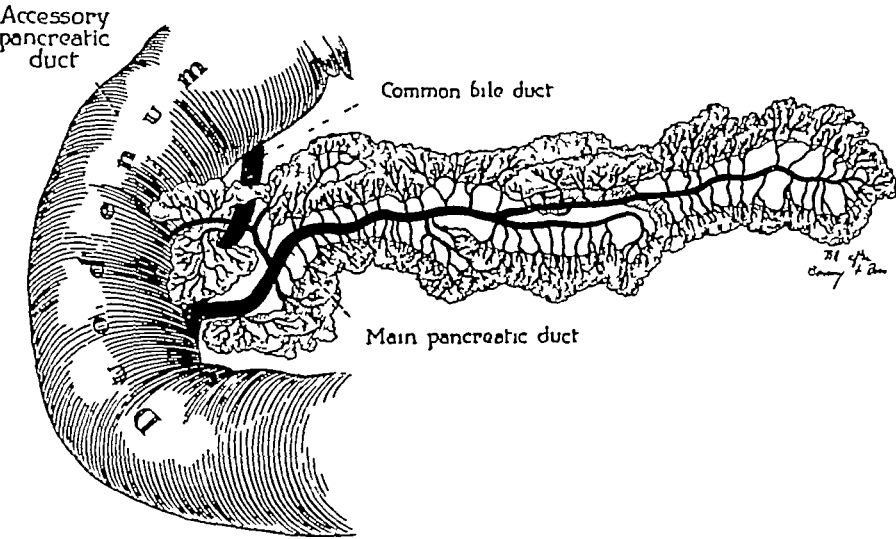


FIG 10 USUAL RELATION OF COMMON BILE DUCT AND PANCREATIC DUCTS



this tonus still more Large amounts (250 to 400 cc ) of HCl of higher concentrations, 0.4 to 0.5 per cent, especially in the case of pernicious anemia patients, affects a different mechanism, the vomiting reflex or possibly merely gagging

TABLE 5  
*Regurgitation with fractional test meals*

| Experiment number | Diagnosis            | Fasting content |         | H <sub>2</sub> O      |          |          |                 | Fraction |   |   |   |   |   | Nature of meal |
|-------------------|----------------------|-----------------|---------|-----------------------|----------|----------|-----------------|----------|---|---|---|---|---|----------------|
|                   |                      | Bile            | Trypsin | Total number of tests | Number + | Number - |                 | 1        | 2 | 3 | 4 | 5 | 6 |                |
| 14                | Duodenal ulcer       | -               | +       | 7                     | 5        | 2        | Bile<br>Trypsin | -<br>+   | + | + | + |   |   | Cane sugar     |
| 15                | Retropentoneal tumor | +               | +       | 10                    | 7        | 3        | Bile<br>Trypsin | -<br>-   | - | + |   |   |   | Glucose        |
| 16                | Asthma               | -               | +       | 6                     | 4        | 2        | Bile<br>Trypsin | -<br>+   | - | - | - | - | - | Albumin        |
| 17                | Compression myelitis | -               | +       | 2                     | 1        | 1        | Bile<br>Trypsin | -<br>+   | - | - | - | - | - | Glucose        |
| 18                | Normal               | -               | +       | 3                     | 2        | 1        | Bile<br>Trypsin | -<br>-   | - | - | - | - | + | Glucose        |
| 19                | Simple achylia       | +               | +       | 11                    | 9        | 2        | Bile<br>Trypsin | -<br>-   | + | + | + | - | - | Glucose        |
| 20                | Simple achylia       | +               | +       | 6                     | 4        | 2        | Bile<br>Trypsin | -<br>+   | - | - | - | - | + | Albumin        |
| 21                | Pyloric obstruction  | +               | +       | 2                     | 2        | 0        | Bile<br>Trypsin | -<br>-   | - | + | + |   |   | Gruel          |
| 22                | Pernicious anemia    | +               | +       | 6                     | 6        | 0        | Bile<br>Trypsin | -<br>+   | - | - | - | - |   | Gruel          |

These views are supported by our findings with fractional test meals In table 5 are recorded the data from 9 such experiments, either with solutions of sugar or albumin or gruel

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|-------------------|-----------------------|-----------------|---------|-----------------------|---|---|-----------------|----------|---|---|---|---|---|----------------|
|                   |                       | Bile            | Trypsin | Total number of tests | + | - |                 | 1        | 2 | 3 | 4 | 5 | 6 |                |
|                   |                       |                 |         |                       |   |   |                 |          |   |   |   |   |   |                |
| 14                | Duodenal ulcer        | -               | +       | 7                     | 5 | 2 | Bile<br>Trypsin | -<br>+   | + | + | + |   |   | Cane sugar     |
| 15                | Retroperitoneal tumor | +               | +       | 10                    | 7 | 3 | Bile<br>Trypsin | -<br>-   | - | + |   |   |   | Glucose        |
| 16                | Asthma                | -               | +       | 6                     | 4 | 2 | Bile<br>Trypsin | -<br>+   | - | + | + | + | + | Albumin        |
| 17                | Compression myelitis  | -               | +       | 2                     | 1 | 1 | Bile<br>Trypsin | -<br>+   | - | + | + | + | + | Glucose        |
| 18                | Normal                | -               | +       | 3                     | 2 | 1 | Bile<br>Trypsin | -<br>-   | - | - | - | - | + | Glucose        |
| 19                | Simple achylia        | +               | +       | 11                    | 9 | 2 | Bile<br>Trypsin | -<br>-   | + | + | + | - | - | Glucose        |
| 20                | Simple achylia        | +               | +       | 6                     | 4 | 2 | Bile<br>Trypsin | -<br>+   | - | + | + | + | + | Albumin        |
| 21                | Pyloric obstruction   | +               | +       | 2                     | 2 | 0 | Bile<br>Trypsin | -<br>-   | - | + | + |   |   | Gruel          |
| 22                | Pernicious anemia     | +               | +       | 6                     | 6 | 0 | Bile<br>Trypsin | -<br>+   | - | + | + | + |   | Gruel          |

These views are supported by our findings with fractional test meals In table 5 are recorded the data from 9 such experiments, either with solutions of sugar or albumin or gruel



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*tion limit*, urea excretion proceeds at maximum speed, and the output per minute represents the urea content of a maximum blood volume. This blood volume, averaging in normal men about 75 cc per minute, we shall for convenience term the *maximum blood urea clearance*, or simply the *maximum clearance*. It represents the volume of blood which one minute's excretion suffices to clear of urea when the urine volume is large enough to permit a maximum urea output. The value of the maximum clearance,  $C_m$ , is calculated from the observed urea concentrations of the blood and urine,  $B$  and  $U$ , and the urine volume,  $V$ , in cubic centimeters per minute, by the formula,

$$\text{Maximum clearance} = C_m = \frac{U V}{B}$$

The concentration ratio,  $\frac{U}{B}$ , indicates the number of cubic centimeters of blood the urea content of which is represented in 1 cc of urine.  $\frac{U}{B} \times V$  therefore indicates the number of cubic centimeters of blood represented in the urea content of the  $V$  cubic centimeters of urine excreted in 1 minute.

*Below the augmentation limit* the volume of blood, the urea content of which is represented in one minute's excretion, (the blood urea clearance per minute) is not a constant, but varies, on the average, in proportion to the square root of the urine volume. In order to compare excretions below the augmentation limit, therefore, they must either be observed with a standard, constant, urine volume output, or, if observed with other urine volumes, the excretion rates must be corrected for the urine volume effect. It is practically impossible to fix the urine volume at a definite standard, but, by means of the square root rule of Austin, Stillman, and Van Slyke, the urea excretion that would accompany such a standard urine volume can be calculated from the excretion measured with any other volume below the augmentation limit.

The formula for the calculation is developed as follows:

If  $C$  is the observed blood urea clearance (the cubic centimeters of blood, the urea content of which is excreted in 1 minute) with any

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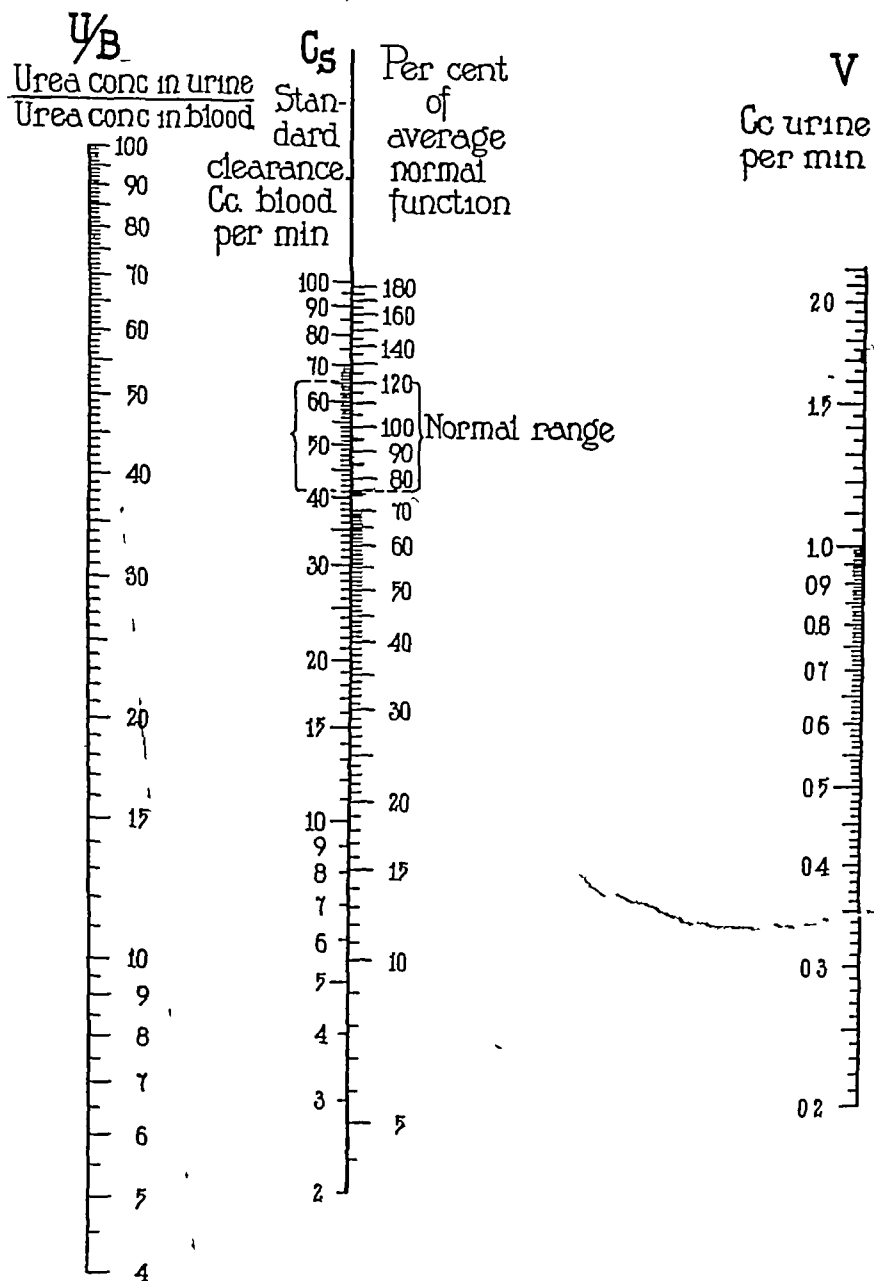


FIG 1 LINE CHART FOR CALCULATING MAXIMUM BLOOD UREA CLEARANCE  
 $C_m = \frac{U V}{B}$ , FROM  $U$ ,  $B$ , AND VALUES OF  $V$  ABOVE THE  
 AUGMENTATION LIMIT

Connect observed  $U/B$  and  $V$  values by a straight line. Where the line cuts the inner scale read  $C_m$  value or per cent of average normal renal function.

For subjects differing markedly from usual adult size, a correction is introduced by multiplying the observed  $V$  value by the factor  $\frac{1.73}{\text{sq m surface area}}$  (see next paper), and using the  $V$  value thus corrected for the calculation of  $C_m$ .

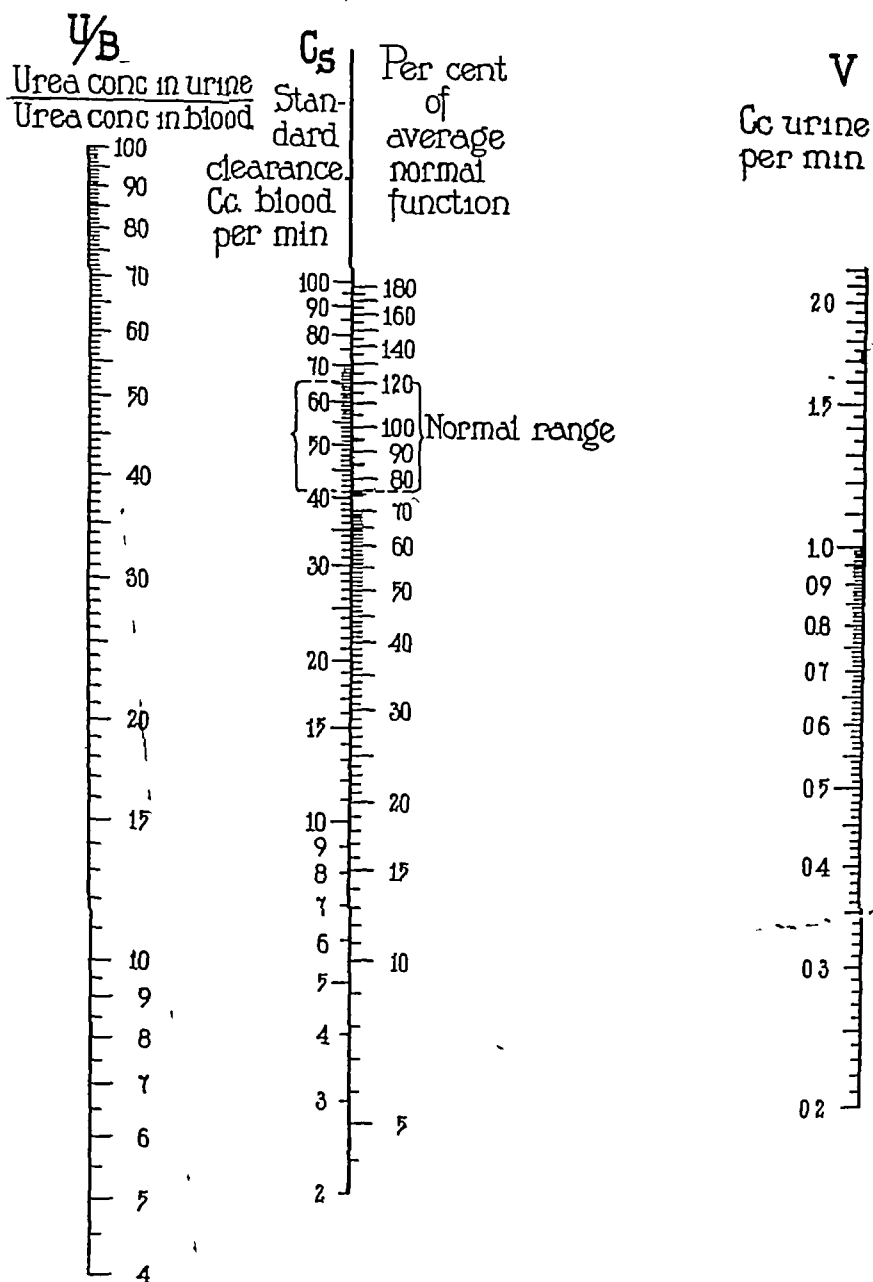


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*of urea excretion with high urine volumes* The maximum clearance is normally about 40 per cent greater than the standard clearance, the mean values being 75 cc of blood per minute for the maximum and 54 cc for the standard. Usually, though not always, in pathological conditions both values are affected to approximately the same degree.

For use in the above formulae for calculating  $C_s$  and  $C_m$ , any convenient units of urea or urea N concentration, e.g. grams per liter, milligram per 100 cc, may be used to express the urea concentrations,  $U$  and  $B$  so long as the *same* unit is used for both  $U$  and  $B$ . This follows from the fact that in each formula  $U$  and  $B$  appear only in the ratio  $\frac{U}{B}$ , so that both  $U$  and  $B$  may be multiplied by any factor

without changing the value of  $\frac{U}{B}$  ratio, or of the  $C_s$  or  $C_m$  calculated therefrom.

The unit for expressing values of  $V$ , however, can not be changed without changing the numerical values of  $C_s$  and  $C_m$ .

#### CALCULATION OF CLEARANCE VALUES

If the urine volume exceeds 2 cc per minute, as observed in an adult, or as corrected for body size (see next paper) in a child, the *maximum clearance* is calculated.

If the volume thus observed or corrected is less than 2 cc per minute, the *standard clearance* is calculated.

It is advantageous as a rule to calculate both clearances in percentages of the mean normal  $C_s$  and  $C_m$ . Urea excretions observed with ordinary urine volumes and calculated in terms of  $C_s$  are thus rendered directly comparable with excretions observed with large urine volumes and hence calculated in terms of  $C_m$ . Furthermore the percentage values thus calculated express directly percentages of average normal renal efficiency.

The percentage of average normal  $C_m$  is obtained by dividing the absolute  $C_m$  value by the mean normal  $C_m$ , 75, and multiplying by 100. Similarly the percentage of average normal  $C_s$  is obtained by dividing the absolute  $C_s$  by 54 and multiplying by 100.

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$$C_m = \frac{UV}{B} = \frac{321 \times 3.5}{15.6} = 72 \text{ cc of blood cleared of urea per minute}$$

$$\text{Per cent of average normal function} = 1.33 \times 72 = 96 \text{ per cent}$$

*Example of calculation of a normal standard clearance*

$$\text{Blood urea N} = 14.7 \text{ mgm. per 100 cc} = B$$

$$\text{Urine urea N} = 750 \text{ mgm. per 100 cc.} = U$$

$$\text{Urine volume} = 50 \text{ cc per hour}$$

$$= 0.83 \text{ cc per minute} = V$$

$$C_s = \frac{U\sqrt{V}}{B} = \frac{750 \times 0.91}{14.7} = 46 \text{ cc of blood cleared of urea per minute}$$

$$\text{Per cent of average normal function} = 1.85 \times 46 = 85 \text{ per cent}$$

*Technique for determining the blood urea clearance as a measure of renal efficiency* The necessary data are the concentrations of urea in blood and urine, and the volume of urine excreted in a measured time. The manner in which these 3 values are secured may be varied to suit conditions. As a routine procedure, however, we have found the following satisfactory:

The subject is not subjected to any previous routine, except that vigorous exercise is avoided and the previous meal should be a moderate one, preferably without coffee, which Addis and Drury (1923) have found may increase the blood urea clearance. The most desirable time of day, when excretion is least liable to fluctuations, is found according to MacKay (1928) in the hours between breakfast and lunch. The patient remains quiet while the urine is collected during two succeeding periods of 1 hour each. The chief source of error is probably the possibility of incomplete emptying of the bladder, either at the beginning or end of a period. The collection of two urine specimens affords a check on this factor. A few minutes before the end of the first hour a blood sample is drawn. Its urea content is used for calculation of the clearances during both periods. This usage is permissible, because under the conditions of the test the blood urea does not change greatly during an hour.

The maximum clearance is calculated if the urine volume observed in an adult, or if the corrected volume  $V \times \frac{1.73}{\text{Sq m surface area}}$

$$C_m = \frac{UV}{B} = \frac{321 \times 35}{156} = 72 \text{ cc of blood cleared of urea per minute}$$

Per cent of average normal function =  $1.33 \times 72 = 96$  per cent

*Example of calculation of a normal standard clearance*

Blood urea N = 14.7 mgm. per 100 cc =  $B$

Urine urea N = 750 mgm. per 100 cc. =  $U$

Urine volume = 50 cc per hour

= 0.83 cc per minute =  $V$

$$C_s = \frac{U\sqrt{V}}{B} = \frac{750 \times 0.91}{14.7} = 46 \text{ cc of blood cleared of urea per minute}$$

Per cent of average normal function =  $1.85 \times 46 = 85$  per cent

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very large doses of adrenalin. The effect of adrenalin, however, was shown in rabbits by Addis, Barnett, and Shevky (1918) to vary with the dosage, up to a certain maximum it increased urea output, but greater amounts depressed the output. Ordinarily Addis (1917) believed that adrenalin and pituitrin act as antagonists in regulating renal activity.

Such influences may vary the blood clearance per minute in either of two ways. They may vary the renal blood flow without altering the percentage of blood urea removed at each passage through the kidneys. Or they may so influence the activity of renal cells that variations do result in the percentage of blood urea removed at each passage. The questions, whether and how the percentage of urea removed from the blood in the kidneys can be influenced, awaits experimental proof.

It is evident that the urea excretion rate is influenced by other factors in addition to blood urea content and urine volume, and that an erroneous impression would be created by the clearance formulae if they were assumed to express with mathematical exactness the complete effects of all factors influencing urea excretion. The width of the range of normal variation indicates the contrary. The formulae are only expressions of the effects of two factors, blood urea content and urine volume, which are in continual action and appear to be ordinarily of chief importance in regulating the urea output.

To minimize variations due to other factors Addis (1922) in determining the maximum clearance gives water and urea to the fasting subject at the beginning of a 6 hour period, and analyzes specimens of blood and urine collected during the last 3 hours of the period, during which diuresis is maintained by water drinking. In determining the standard clearance in this laboratory we have thus far set no conditions, except that the subject should be at rest and should have avoided coffee and other obvious diuretics during the preceding hours of the day. The limits of variation in our results, reported below, apply to these conditions. It appears possible that by standardizing conditions more completely the range of variation could be narrowed.

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output per 24 hours, and noted the rapidity with which the superimposed amount of nitrogen was excreted. The procedure was, however, laborious, the results not very consistent. The method was abandoned, to be revived occasionally by later authors.

Other authors turned their attention to the blood urea, and neglected the excretion. The determination of blood urea was introduced into clinical medicine by Strauss (1902) and by Widal and Javal (1904). For diagnostic purposes determination of blood urea concentration has an advantage over determination of urine concentration, in that with ordinary urine volumes the blood figure is less dependent on fluctuations of water output. Other factors being constant, however, the blood urea content is proportional to the rate of protein catabolism. If a given subject breaks down into urea half as much protein daily his average blood urea will be half as high, given a constant urine volume. If the urine volume increases within the ordinary range (below the augmentation limit), the blood urea will be further diminished, increased water output washing out more urea from the blood. Both of these factors are likely to be operative in nephritis to prevent a rise in blood urea proportional to renal destruction. MacKay and MacKay (1927) in fact report data (which our own confirm) showing that many nephritics do not show blood ureas definitely above the normal maximum until more than 60 per cent of renal function has been lost.

The conception of comparing simultaneous urea determinations in blood and urine was introduced by Gréhan (1904) who used the concentration ratio  $\frac{U}{B}$  as an expression of renal functional ability. However, the immense effects of urine volume changes on the urea concentration,  $U$ , in urine were not considered, in consequence of which even approximate constancy can not be obtained with this ratio. The use of the  $\frac{U}{B}$  ratio was revived by Harrison (1922), who emphasized that the most consistent results were gained when the urine volumes were below 150 to 100 cc per hour. This restriction reduces the inconsistencies introduced into the  $\frac{U}{B}$  ratio by urine volume changes, but also limits the conditions under which observations can be made.

Ambard and Weill (1912) were the first to include both urea output and urine volume in attempting quantitatively to relate urea excretion to blood content. They found that urea excretion in normal subjects, and also in nephritics, was governed by two laws, relating output to blood and urine concentrations respectively. These laws were combined into the urea excretion formula of Ambard and Weill (1912), which, with numerical constants omitted, is

$$K = \frac{B}{\sqrt{D} \sqrt{U}}$$

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In the present paper we confirm these results on normal subjects, and in an accompanying paper we show that they hold true for nephritics also

H MacLean and de Wesselow (1919, 1920) in the interest of simplicity reverted to a single determination, the urea concentration in the urine, as a test of renal function. These authors prescribed certain standard conditions for its determination, designed to make the values more consistent. They gave 15 grams of urea with 100 cc of water, and noted whether or not the urine urea concentration in the 2 subsequent hours rose above 2 per cent. If it did, they considered the kidneys fairly efficient. Gross errors due to dilute urines were excluded by rejecting tests in which the second hour's urine volume exceeded 150 cc. Their procedure was admirably adapted to its primary purpose, the rapid examination of large numbers of soldiers. In the study of nephritic patients, however, the method invites error by neglect of the blood urea. For example, if urinary function is so low that only a tenth the normal blood volume is cleared of urea per hour, the urea output will nevertheless be normal if the blood urea concentration is ten-fold the ordinary. Hence the urinary concentration will also be normal, if the volume is not increased. For this reason, in the terminal stages of nephritis, with high blood urea content, a urinary urea concentration within ordinary normal ranges may be observed, despite tremendously reduced renal ability.<sup>2</sup> The interpretation of figures for urea concentration in urine is therefore uncertain, unless the blood urea content is known, as well as the urine volume.

The historical sequence in which the different urea determinations were introduced as indicators of renal function, and the conditions under which they were best applicable, are summarized in table 1.

*Numerical relation of the present standard clearance to previously used forms of the Austin-Stillman-Van Slyke formula.* The formula  $\frac{U}{B} \sqrt{V}$

expresses the number of cubic centimeters of blood of which the urea content is concentrated into 1 cc of urine, when urine excretion is at the average normal rate of 1 cc per minute. The mean normal numerical value of 54 indicates that under these conditions the kidneys concentrate the blood urea 54-fold. The standard clearance thus may be interpreted as a measure of the concentrating power, as well as the excreting ability, of the kidney. For this reason the value now called the standard clearance has, in a number of papers from this laboratory (e g Hiller, McIntosh, and Van Slyke (1927)) been called the "*concentration index*." The term "standard clearance" is at pres-

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ent preferred, partly because when used in conjunction with "maximum clearance" it suggests more clearly the difference in conditions under which the two respective urea excretion rates are determined

In the above papers the formula used in calculating the "index" was  $\frac{U}{B} \sqrt[4]{\frac{V}{W}}$  instead of  $\frac{U}{B} \sqrt{V}$ . However, in the  $\frac{V}{W}$  ratio used the volume unit was cubic centimeters per hour per kilogram, which, for a person of 60 kgm weight, is the same as cubic centimeters per minute. Hence the values of  $\frac{U}{B} \sqrt[4]{\frac{V}{W}}$  in the above papers are approximately interchangeable with those of the present  $C_s = \frac{U}{B} \sqrt{V}$ . They deviate therefrom in proportion as  $\sqrt{W}$  deviates from  $\sqrt{60}$ , but the fact that unusually low or high body weights influence the value  $\frac{U}{B} \sqrt[4]{\frac{V}{W}}$  only in proportion to their square roots, and not their first powers, diminishes the effect on the calculated clearance. E.g., a person of 50 kgm would weigh 17 per cent less than one of 60, but the effect of this weight difference on the value of the index  $\frac{U}{B} \sqrt[4]{\frac{V}{W}}$  is only 9 per cent. Our present practice, discussed in the next paper, is to correct for wide divergence from average size by multiplying  $V$  by the factor  $\frac{1.73}{\text{Sq m surface area}}$ .

The standard clearance  $\frac{U}{B} \sqrt{V}$  is, except for omission of the weight correction, identical with the excretion constant  $\frac{D}{B \sqrt{1/W}}$  of Austin, Stillman and Van Slyke. If in  $\frac{D}{B \sqrt{1/W}}$  the factor  $D$  is replaced by its equivalent,  $UV$ , the formula changes to  $\frac{U}{B} \sqrt[4]{\frac{V}{W}}$ . Omission of the weight correction,  $W$ , simplifies it to  $\frac{U}{B} \sqrt{V}$ . The original numerical values of the excretion constant  $\frac{D}{B \sqrt{1/W}}$ , or  $\frac{U}{B} \sqrt[4]{\frac{V}{W}}$ , of these authors differed from the present clearance, and from the above discussed concentration index, because a different urine volume unit,  $\frac{V}{W}$  = liters per 24 hours per kilogram, was used. A given excretion rate expressed in cubic centimeters per minute is represented by a figure  $\frac{1000 W}{1440}$ , or 0.694  $W$ , times as large as that ex-

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As opinions still are divided we have considered it desirable to increase the number of observations covering the influence of urine volume on urea excretion in normal subjects. We have attempted to limit the factors influencing excretion as nearly as practicable to one, water. In some of the experiments data were also obtained on the effect of urea ingestion, which, however, was not observed to affect significantly the clearance values obtained.

#### EXPERIMENTAL

We have examined 5 normal persons between 20 and 30 years of age, all in good health and without any history of kidney disease. We also have reexamined another normal subject, now 44 years of age, (Van Slyke), on whom data were first published by Austin, Stillman, and Van Slyke, six years ago.

During each experiment (except those on Van Slyke) the person examined was kept in bed. The reasons for this were, first, that changes of position are said to influence the water excretion through the kidneys (White, Rosen, Fischer and Wood (1926)) and, second, that the kidney function of patients is nearly always examined while they are in bed, so it seems more correct to compare them with normals studied under similar conditions.

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#### RESULTS AND DISCUSSION

The conditions and results of all our experiments are given in tables 1 to 4

The results for each of the 6 subjects investigated by us, and for one other from the literature (Rehberg, 1926), have been plotted in figures 3 to 9 with clearance values as ordinates and  $\sqrt{V}$  as abscissae. In order to simplify the plotting by obtaining straight line curves we have laid off as abscissae values of the square root of the urine volume. According to the square root rule, this procedure should enable one to express the relationship between urine volume and blood clearance as a rising straight line below the augmentation limit, and it will be seen in the graphs that such is the case. Above the augmentation limit volume has no effect, and the excretion curve becomes a horizontal line.

The curves have been drawn in the following manner. The mean value of the clearance  $\frac{UV}{B}$ , in cubic centimeters of blood containing the amount of urea excreted per minute, for all points above the augmentation limit is taken, and at the corresponding height above the horizontal axis, and parallel to it, a line is drawn. Then for all points to the left of the augmentation limit the standard clearance  $\frac{U}{B} \sqrt{V}$  is calculated, and the mean value is taken. This average determines the height of the curve at  $V = 1$  cc. Through the corresponding point on the vertical line representing  $V = 1$  cc, and through the zero point, a straight line is drawn. The position of the augmentation limit is calculated as the intersection point between this slanting line and the horizontal line first drawn.

In this way we have calculated augmentation limits from the data given by Austin, Stillman, and Van Slyke on Austin and Van Slyke, our own data on six normal subjects, and finally the data given by Rehberg (1926) on himself, that were collected by him for quite other reasons, but can be used for our purpose as well.

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TABLE 2—Continued

| Experiments               | Time  | V<br>Urine<br>volume | U<br>Urine<br>urea<br>nitrogen | B<br>Blood<br>urea<br>nitrogen | $\frac{UV}{B}$<br>Ob-<br>served<br>clear-<br>ance* | $C_s = \frac{U\sqrt{V}}{B}$<br>Standard<br>clearance,<br>calculated for<br>$V = 1$ , from<br>observed<br>clearances<br>below aug-<br>mentation<br>limits | Per cent of<br>average<br>normal<br>clearance,<br>taken as<br>$C_s = 54$ ,<br>$C_m = 75$ |
|---------------------------|-------|----------------------|--------------------------------|--------------------------------|--|--|--|
|                           |       | cc per<br>minute     | mg per<br>100 cc               | mg per<br>100 cc               | cc blood<br>per<br>minute                          | cc blood per<br>minute   | per cent   |
| Experiment Number 1       | 9-10  | 7 17                 | 415                            | 39 3                           | 75 5*  |  | 101*   |
| J F M                     | 10-11 | 8 08                 | 324                            | 38 5                           | 68 0*  |  | 91*  |
| 7 a m, 30 grams urea and  | 11-12 | 4 00                 | 842                            | 46 6                           | 72 3*  |  | 96*  |
| 500 cc. of water 10 and   | 12-1  | 2 42                 | 1321                           | 44 9                           | 71 2*  |  | 95*  |
| 11 a.m., 12 noon and 1    | 1-2   | 1 63                 | 1398                           | 36 7                           | 62 2   | 48 6   | 90   |
| p m., 5 grams, urea each  | 2-3   | 1 67                 | 1273                           | 42 5                           | 49 8   | 38 7   | 72   |
| time                      |       |                      |                                |                                |  |  |  |
| Experiment Number 8       | 9-10  | 0 75                 | 1568                           | 25 1                           | 46 8   | 54 1   | 100  |
| J F M                     | 10-11 | 0 92                 | 1564                           | 29 0                           | 49 5   | 51 8   | 96   |
| 7 15 a m, 15 grams urea   | 11-12 | 1 08                 | 1260                           | 29 9                           | 45 7   | 43 8   | 81   |
| 12 45 p m, lunch 1 and    | 12-1  | 0 60                 | 1185                           | 24 6                           | 29 0   | 37 3   | 69   |
| 2 p m, 1000 cc of water   | 1-2   | 1 03                 | 1366                           | 24 7                           | 57 2   | 56 2   | 104  |
| each time                 | 2-3   | 8 58                 | 193                            | 21 9                           | 75 7*  |  | 101*   |
| Experiment Number 3       | 9-10  | 1 67                 | 1068                           | 25 8                           | 69 2   | 53 5   | 99   |
| A H                       | 10-11 | 1 42                 | 1034                           | 25 5                           | 57 5   | 48 3   | 89   |
| 7 a m, 15 grams urea 11   | 11-12 | 3 67                 | 593                            | 32 3                           | 67 3*  |  | 90*  |
| a m, 20 grams urea and    | 12-1  | 7 87                 | 264                            | 40 0                           | 52 2*  |  | 70*  |
| 200 cc of water 1 30      | 1-2   | 2 08                 | 1095                           | 34 2                           | 67 0   | 46 2   | 85   |
| p m, lunch and 200 cc of  | 2-3   | 2 42                 | 901                            | 31 7                           | 68 8*  |  | 92*  |
| water                     |       |                      |                                |                                |  |  |  |
| Experiment Number 25      | 9-10  | 0 57                 | 679                            | 13 5                           | 28 5   | 37 9   | 70   |
| A H                       | 10-11 | 0 57                 | 747                            | 13 2                           | 32 0   | 42 7   | 79   |
| 8 30, breakfast. 12 noon, | 11-12 | 0 63                 | 800                            | 12 6                           | 40 2   | 50 4   | 93   |
| lunch and 1000 cc of      | 12-1  | 1 63                 | 495                            | 13 3                           | 60 8   | 47 5   | 88   |
| water 1 p.m., 500 cc of   | 1-2   | 10 83                | 87 3                           | 13 6                           | 77 5*  |  | 103*   |
| water                     | 2-3   | 9 07                 | 88 8                           | 13 1                           | 61 5*  |  | 82*  |
| Experiment Number 5       | 10-11 | 0 60                 | 1074                           | 15 6                           | 41 3   | 53 3   | 99   |
| W N                       |       |                      |                                |                                |  |  |  |
| 7 a m, breakfast and 15   |       |                      |                                |                                |  |  |  |
| grams urea in 75 cc. of   |       |                      |                                |                                |  |  |  |
| water Could not void      |       |                      |                                |                                |  |  |  |
| on time                   |       |                      |                                |                                |  |  |  |

TABLE 2—Continued

| Experiments               | Time  | $V$<br>Urine<br>volume | $U$<br>Urine<br>urea<br>nitrogen | $B$<br>Blood<br>urea<br>nitrogen | $\frac{UV}{B}$<br>Ob-<br>served<br>clear-<br>ance* | $C_s = \frac{U\sqrt{V}}{B}$<br>Standard<br>clearance,<br>calculated for<br>$V = 1$ , from<br>observed<br>clearances<br>below aug-<br>mentation<br>limits | Per cent of<br>average<br>normal<br>clearance,<br>taken as<br>$C_s = 54$ ,<br>$C_m = 75$ |
|---------------------------|-------|------------------------|----------------------------------|----------------------------------|--|--|--|
|                           |       | cc per<br>minute       | mg per<br>100 cc                 | mg per<br>100 cc                 | cc blood<br>per<br>minute                          | cc blood per<br>minute   | per cent   |
| Experiment Number 1       | 9-10  | 7 17                   | 415                              | 39 3                             | 75 5*  |  | 101*   |
| J F M                     | 10-11 | 8 08                   | 324                              | 38 5                             | 68 0*  |  | 91*  |
| 7 a m, 30 grams urea and  | 11-12 | 4 00                   | 842                              | 46 6                             | 72 3*  |  | 96*  |
| 500 cc. of water 10 and   | 12-1  | 2 42                   | 1321                             | 44 9                             | 71 2*  |  | 95*  |
| 11 a.m., 12 noon and 1    | 1-2   | 1 63                   | 1398                             | 36 7                             | 62 2   | 48 6   | 90   |
| p m., 5 grams, urea each  | 2-3   | 1 67                   | 1273                             | 42 5                             | 49 8   | 38 7   | 72   |
| time                      |       |                        |                                  |                                  |  |  |  |
| Experiment Number 8       | 9-10  | 0 75                   | 1568                             | 25 1                             | 46 8   | 54 1   | 100  |
| J F M                     | 10-11 | 0 92                   | 1564                             | 29 0                             | 49 5   | 51 8   | 96   |
| 7 15 a m, 15 grams urea   | 11-12 | 1 08                   | 1260                             | 29 9                             | 45 7   | 43 8   | 81   |
| 12 45 p m, lunch 1 and    | 12-1  | 0 60                   | 1185                             | 24 6                             | 29 0   | 37 3   | 69   |
| 2 p m, 1000 cc of water   | 1-2   | 1 03                   | 1366                             | 24 7                             | 57 2   | 56 2   | 104  |
| each time                 | 2-3   | 8 58                   | 193                              | 21 9                             | 75 7*  |  | 101*   |
| Experiment Number 3       | 9-10  | 1 67                   | 1068                             | 25 8                             | 69 2   | 53 5   | 99   |
| A H                       | 10-11 | 1 42                   | 1034                             | 25 5                             | 57 5   | 48 3   | 89   |
| 7 a m, 15 grams urea 11   | 11-12 | 3 67                   | 593                              | 32 3                             | 67 3*  |  | 90*  |
| a m, 20 grams urea and    | 12-1  | 7 87                   | 264                              | 40 0                             | 52 2*  |  | 70*  |
| 200 cc of water 1 30      | 1-2   | 2 08                   | 1095                             | 34 2                             | 67 0   | 46 2   | 85   |
| p m, lunch and 200 cc of  | 2-3   | 2 42                   | 901                              | 31 7                             | 68 8*  |  | 92*  |
| water                     |       |                        |                                  |                                  |  |  |  |
| Experiment Number 25      | 9-10  | 0 57                   | 679                              | 13 5                             | 28 5   | 37 9   | 70   |
| A H                       | 10-11 | 0 57                   | 747                              | 13 2                             | 32 0   | 42 7   | 79   |
| 8 30, breakfast. 12 noon, | 11-12 | 0 63                   | 800                              | 12 6                             | 40 2   | 50 4   | 93   |
| lunch and 1000 cc of      | 12-1  | 1 63                   | 495                              | 13 3                             | 60 8   | 47 5   | 88   |
| water 1 p.m., 500 cc of   | 1-2   | 10 83                  | 87 3                             | 13 6                             | 77 5*  |  | 103*   |
| water                     | 2-3   | 9 07                   | 88 8                             | 13 1                             | 61 5*  |  | 82*  |
| Experiment Number 5       | 10-11 | 0 60                   | 1074                             | 15 6                             | 41 3   | 53 3   | 99   |
| W N                       |       |                        |                                  |                                  |  |  |  |
| 7 a m, breakfast and 15   |       |                        |                                  |                                  |  |  |  |
| grams urea in 75 cc. of   |       |                        |                                  |                                  |  |  |  |
| water Could not void      |       |                        |                                  |                                  |  |  |  |
| on time                   |       |                        |                                  |                                  |  |  |  |

TABLE 2—Continued

| Experiments                  | Time  | V<br>Urine<br>volume | U<br>Urine<br>urea<br>nitrogen | B<br>Blood<br>urea<br>nitrogen | $\frac{UV}{B}$<br>Ob-<br>served<br>clear-<br>ance* | $C_s = \frac{U\sqrt{V}}{B}$<br>Standard<br>clearance,<br>calculated for<br>$V = 1$ , from<br>observed<br>clearances<br>below aug-<br>mentation<br>limits | Per cent of<br>average<br>normal<br>clearance,<br>taken as<br>$C_s = 54$ ,<br>$C_m = 75$ |
|------------------------------|-------|----------------------|--------------------------------|--------------------------------|--|--|--|
|                              |       | cc per<br>minute     | mg per<br>100 cc               | mg per<br>100 cc               | cc. blood<br>per<br>minute                         | cc per blood<br>minute   | per cent   |
| Experiment Number 28         | 9-10  | 0 97                 | 781                            | 19 4                           | 38 8   | 39 6   | 73   |
| J C B                        | 10-11 | 1 00                 | 731                            | 19 2                           | 38 1   | 38 1   | 71   |
| 7 30 a.m., breakfast.        | 11-12 | 1 25                 | 656                            | 18 9                           | 43 3   | 38 8   | 72   |
| noon, lunch                  | 12-1  | 1 02                 | 642                            | 16 6                           | 39 3   | 39 1   | 72   |
|                              | 1-2   | 0 80                 | 746                            | 17 2                           | 34 7   | 38 8   | 72   |
| Experiment Number 31         | 9-10  | 7 33                 | 119 4                          | 14 7                           | 59 6*  |  | 79*  |
| J C B                        | 10-11 | 7 58                 | 103 3                          | 12 5                           | 62 6*  |  | 83*  |
| 7 30 a.m., breakfast and 500 | 11-12 | 8 75                 | 83 4                           | 12 3                           | 59 3*  |  | 79*  |
| cc. of water 8 40, 10, 11    | 12-1  | 6 67                 | 113 7                          | 11 3                           | 67 2*  |  | 90*  |
| a.m., and 12 noon, 500       | 1-2   | 12 33                | 54 2                           | 11 2                           | 59 6*  |  | 79*  |
| cc. of water each time 12    | 2-3   | 11 67                | 52 2                           | 10 5                           | 58 0*  |  | 77*  |
| noon, lunch 1 p.m., 300      |       |                      |                                |                                |  |  |  |
| cc and 2 p.m., 200 cc of     |       |                      |                                |                                |  |  |  |
| water                        |       |                      |                                |                                |  |  |  |
| Experiment Number 33         | 10-11 | 0 80                 | 765                            | 13 7                           | 44 6   | 49 8   | 92   |
| D V S, 1927                  | 11-12 | 1 33                 | 640                            | 11 6                           | 73 6   | 63 6   | 118  |
| 8 30, breakfast              | 12-1  | 1 07                 | 619                            | 12 7                           | 52 0   | 50 3   | 93   |
| 12 45 p.m., lunch No fluids  | 1-2   | 0 73                 | 775                            | 11 2                           | 50 7   | 59 2   | 110  |
| Cutaneous blood              | 2-3   | 0 50                 | 906                            | 10 3                           | 44 0   | 62 2   | 115  |
|                              | 3-4   | 0 70                 | 806                            | 9 4                            | 60 0   | 71 7   | 133  |
|                              | 4-5   | 0 60                 | 808                            | (9 4)                          | 51 6   | 66 5   | 123  |
| Experiment Number 34         | 9-10  | 6 41                 | 153                            | 13 1                           | 74 8*  |  | 100*   |
| D V S 1927                   | 10-11 | 16 25                | 58 6                           | 12 3                           | 77 4*  |  | 103*   |
| 8 30 a.m., breakfast with    | 11-12 | 13 25                | 86 0                           | 12 3                           | 92 6*  |  | 123*   |
| 800 cc. of water 8 50        | 12-1  | 6 37                 | 137                            | 10 3                           | 84 8*  |  | 113*   |
| and 9 15 a.m. 200 cc.,       | 1-2   | 5 26                 | 173                            | 9 6                            | 94 8*  |  | 126*   |
| 9 20 400 cc., 9 35 10 cc.,   | 2-3   | 1 32                 | 438                            |                                | 60 2   | 52 4   | 97   |
| and 10 40 200 cc., 10 45     | 3-4   | 2 77                 | 281                            | (9 0)                          | 86 4*  |  | 115*   |
| 400 cc. of water 12 30       |       |                      |                                |                                |  |  |  |
| p.m., lunch with 200 cc.     |       |                      |                                |                                |  |  |  |
| of water Venous blood        |       |                      |                                |                                |  |  |  |

TABLE 2—Continued

| Experiments                  | Time  | V<br>Urine<br>volume | U<br>Urine<br>urea<br>nitrogen | B<br>Blood<br>urea<br>nitrogen | $\frac{UV}{B}$<br>Ob-<br>served<br>clear-<br>ance* | $C_s = \frac{U\sqrt{V}}{B}$<br>Standard<br>clearance,<br>calculated for<br>$V = 1$ , from<br>observed<br>clearances<br>below aug-<br>mentation<br>limits | Per cent of<br>average<br>normal<br>clearance,<br>taken as<br>$C_s = 54$ ,<br>$C_m = 75$ |
|------------------------------|-------|----------------------|--------------------------------|--------------------------------|--|--|--|
|                              |       | cc. per<br>minute    | mg. per<br>100 cc.             | mg. per<br>100 cc.             | cc. blood<br>per<br>minute                         | cc. per blood<br>minute  | per cent   |
| Experiment Number 28         | 9-10  | 0 97                 | 781                            | 19 4                           | 38 8   | 39 6   | 73   |
| J C B                        | 10-11 | 1 00                 | 731                            | 19 2                           | 38 1   | 38 1   | 71   |
| 7 30 a.m., breakfast. 12     | 11-12 | 1 25                 | 656                            | 18 9                           | 43 3   | 38 8   | 72   |
| noon, lunch                  | 12-1  | 1 02                 | 642                            | 16 6                           | 39 3   | 39 1   | 72   |
|                              | 1-2   | 0 80                 | 746                            | 17 2                           | 34 7   | 38 8   | 72   |
| Experiment Number 31         | 9-10  | 7 33                 | 119 4                          | 14 7                           | 59 6*  |  | 79*  |
| J C B                        | 10-11 | 7 58                 | 103 3                          | 12 5                           | 62 6*  |  | 83*  |
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| cc. of water 8 40, 10, 11    | 12-1  | 6 67                 | 113 7                          | 11 3                           | 67 2*  |  | 90*  |
| a.m., and 12 noon, 500       | 1-2   | 12 33                | 54 2                           | 11 2                           | 59 6*  |  | 79*  |
| cc. of water each time 12    | 2-3   | 11 67                | 52 2                           | 10 5                           | 58 0*  |  | 77*  |
| noon, lunch 1 p.m., 300      |       |                      |                                |                                |  |  |  |
| cc. and 2 p.m., 200 cc of    |       |                      |                                |                                |  |  |  |
| water                        |       |                      |                                |                                |  |  |  |
| Experiment Number 33         | 10-11 | 0 80                 | 765                            | 13 7                           | 44 6   | 49 8   | 92   |
| D V S, 1927                  | 11-12 | 1 33                 | 640                            | 11 6                           | 73 6   | 63 6   | 118  |
| 8 30, breakfast 12 45        | 12-1  | 1 07                 | 619                            | 12 7                           | 52 0   | 50 3   | 93   |
| p.m., lunch No fluids        | 1-2   | 0 73                 | 775                            | 11 2                           | 50 7   | 59 2   | 110  |
| Cutaneous blood              | 2-3   | 0 50                 | 906                            | 10 3                           | 44 0   | 62 2   | 115  |
|                              | 3-4   | 0 70                 | 806                            | 9 4                            | 60 0   | 71 7   | 133  |
|                              | 4-5   | 0 60                 | 808                            | (9 4)                          | 51 6   | 66 5   | 123  |
| Experiment Number 34         | 9-10  | 6 41                 | 153                            | 13 1                           | 74 8*  |  | 100*   |
| D V S 1927                   | 10-11 | 16 25                | 58 6                           | 12 3                           | 77 4*  |  | 103*   |
| 8 30 a.m., breakfast with    | 11-12 | 13 25                | 86 0                           | 12 3                           | 92 6*  |  | 123*   |
| 800 cc. of water 8 50        | 12-1  | 6 37                 | 137                            | 10 3                           | 84 8*  |  | 113*   |
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| 400 cc. of water 12 30       |       |                      |                                |                                |  |  |  |
| p.m., lunch with 200 cc.     |       |                      |                                |                                |  |  |  |
| of water Venous blood        |       |                      |                                |                                |  |  |  |

The results of these calculations are given in table 4

In addition to the above experiments, in which the complete excretion curves were obtained over the maximum urine volume range, observations with ordinary urine volumes, below the augmentation limit, were made on 9 other normal subjects, and are reported, with the resulting standard clearance values, in table 3. The subjects were young men engaged in such activity as involves ordinary laboratory work.

*The augmentation limit* It is seen from table 4, that the augmentation limit in the 8 normal subjects observed occurs at between 1.67 and 2.55 cc per minute, if the observation made on Van Slyke in 1921 is excluded. The higher augmentation limit in this case, due to a very high average maximum clearance, falls statistically outside the group, since it differs by more than four times the mean error<sup>3</sup> from the average. There were only 4 determinations with high urine volumes in this case (data of Austin, Stillman, and Van Slyke) and they were made while the subject was about the laboratory, and not under the conditions of rest imposed on the subjects used for the analyses reported in this paper. Accordingly additional experiments on the same subject have been performed with the present series of observations, during which the subject was sitting quietly at his desk. The augmentation limit and clearances thus obtained fall within the limits of the rest of our observations. In the calculation of the average augmentation limit and maximum clearance, and the variation for the group of normal subjects, given in tables 3 and 4, only the present figures are used for this subject.

#### NORMAL VALUES AND VARIATIONS OF THE STANDARD AND MAXIMUM BLOOD UREA CLEARANCES

In table 4 are summarized the mean standard clearances of the normal subjects reported in detail in tables 2 and 3, and in addition the standard clearances calculated from previous data of Austin, Stillman and Van Slyke (1921). Similarly in table 5 are summarized

<sup>3</sup> The mean error calculated as the standard deviation,  $\pm \sqrt{\frac{\sum a^2}{n-1}}$ , divided by the square root of the number of observations (fig. 9)

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possible that the difference may be due partly to greater body size in Addis' subjects. He employs 1.82 square meters as the mean surface area (private communication through MacKay), and if the subjects

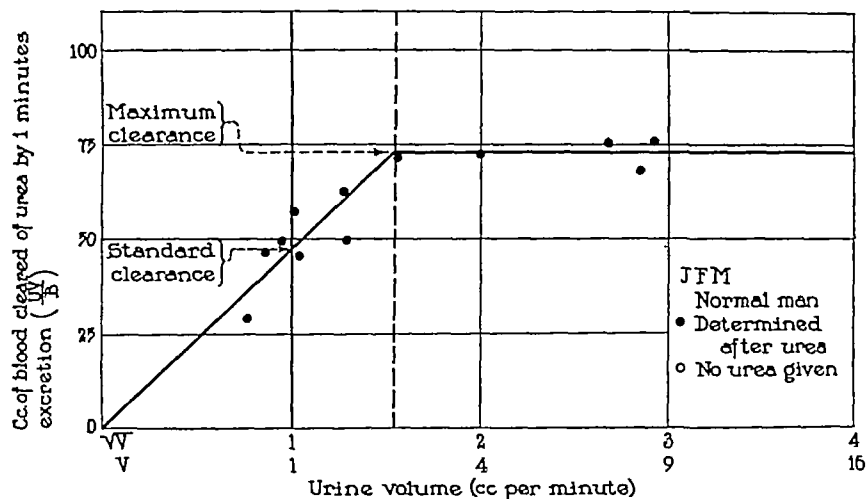


FIG 3 UREA EXCRETION CURVE FROM NORMAL SUBJECT

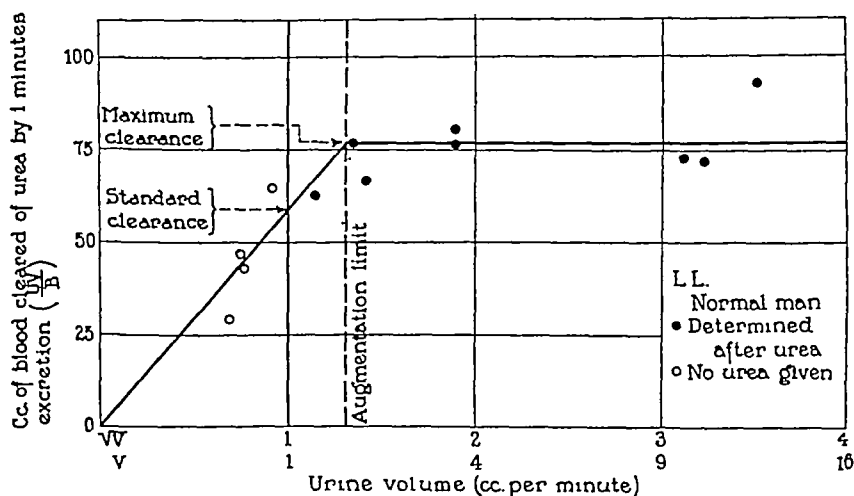


FIG 4 UREA EXCRETION CURVE FROM NORMAL SUBJECT

he reports average as large as this, his mean  $C_c$  of 82 would correspond to one of 78 for subjects of 1.73 square meters area. As the exact heights and weights of Addis' subjects are not obtainable, we have

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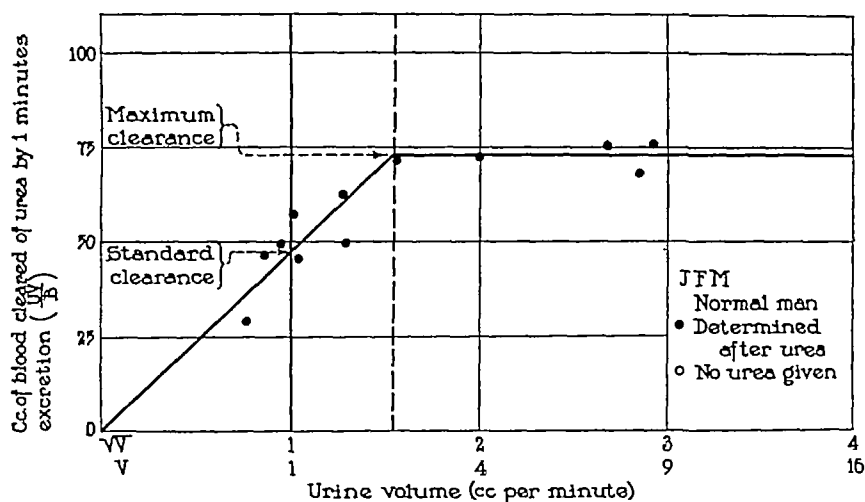


FIG 3 UREA EXCRETION CURVE FROM NORMAL SUBJECT

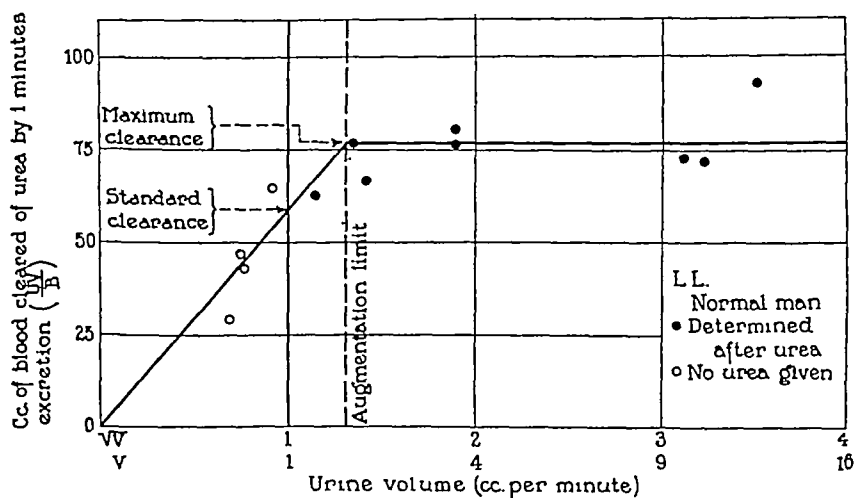


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and 12 therefore cover the area which, in all probability, represents the extreme variation ordinarily to be expected in normal subjects

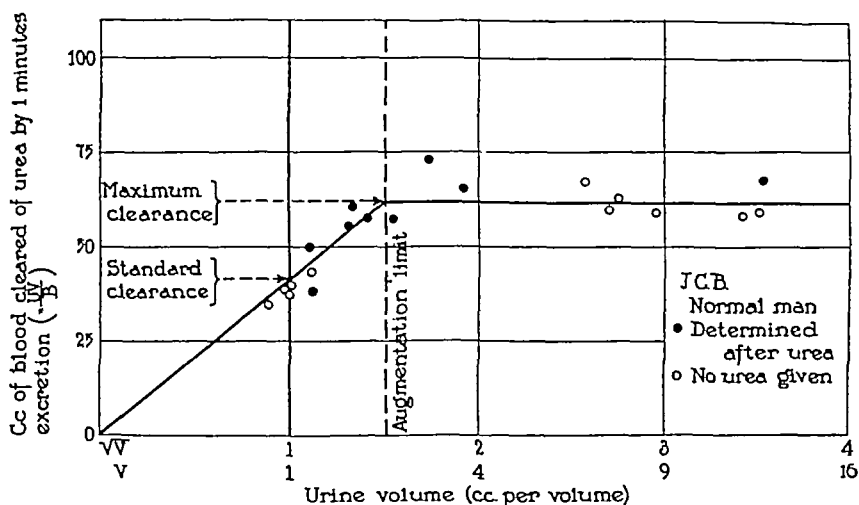


FIG 7 UREA EXCRETION CURVE FROM NORMAL SUBJECT

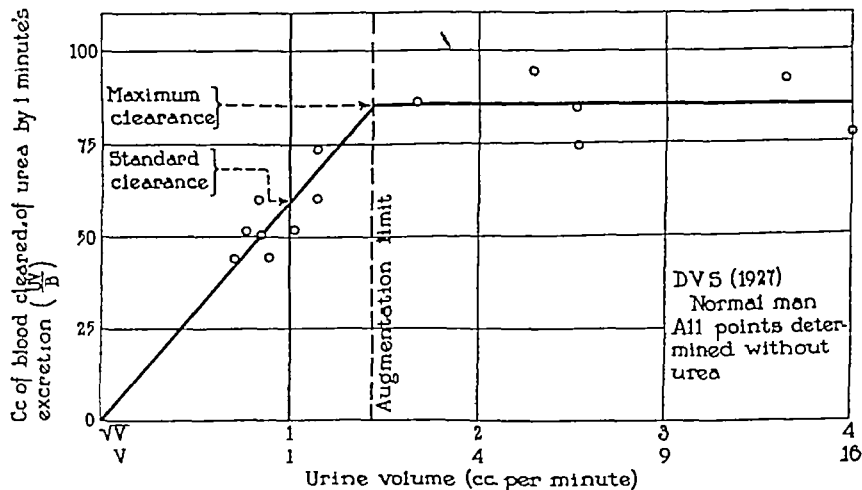


FIG 8 UREA EXCRETION CURVE FROM NORMAL SUBJECT

The results of our experiments, plotted in figures 3 to 8, and those calculated from the data of Rehberg, plotted in figure 9, confirm the conclusions of Austin, Stillman, and Van Slyke. There is a distinct

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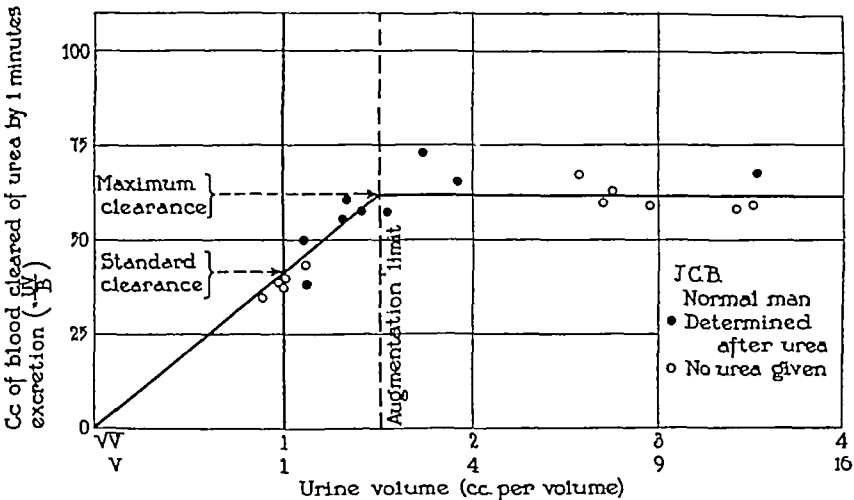


FIG 7 UREA EXCRETION CURVE FROM NORMAL SUBJECT

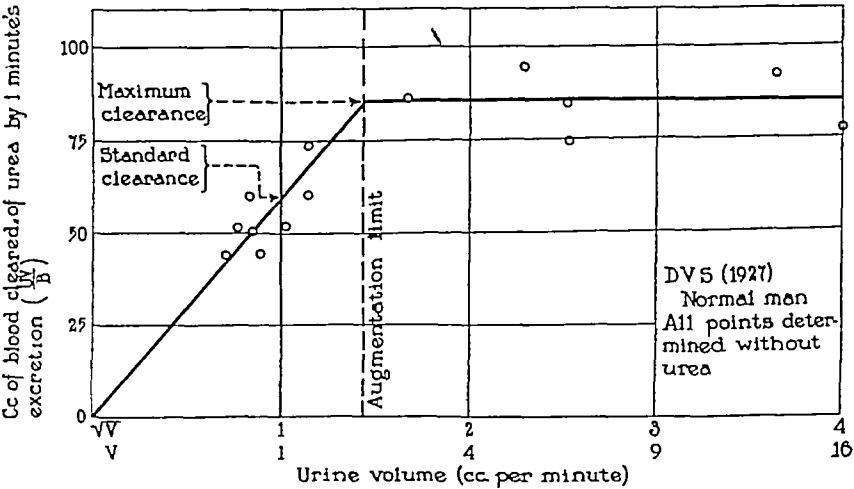


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The results of our experiments, plotted in figures 3 to 8, and those calculated from the data of Rehberg, plotted in figure 9, confirm the conclusions of Austin, Stillman, and Van Slyke There is a distinct

augmentation limit Below it the clearance increases with increasing urine volume, while above it the clearance is independent of urine volume The grouping of points about the slanting portion of the curve indicates that the square-root rule which this portion represents expresses the average effect of urine volume changes No other line or curve could follow the experimental points more closely The deviations of the points are frequently considerable, since other, unknown factors, besides urine volume influence the rate of urea excretion (Addis and Drury, 1923) It is obvious, however, that the

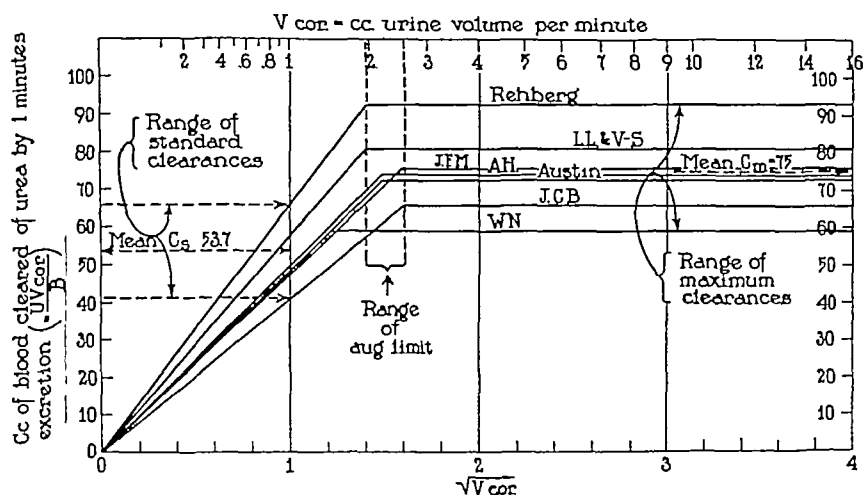


FIG 11

Same curves as in Figure 10, but corrected for body size by multiplying  $V$  values by the correction factor  $\frac{1.73}{\text{square meters surface area}}$

square-root rule is followed with sufficient constancy to make interpretations of urea excretion rates with ordinary urine volumes (below the augmentation limit) much more exact when corrected for the volume effect than they would be if urine volume as a factor were neglected In fact, the deviations of the experimental points from the slanting line representing this rule are not significantly greater than the deviations from the horizontal part of the curves covering ranges in which urine volume changes do not influence output The square-root rule affords as satisfactory a correction for urine volume

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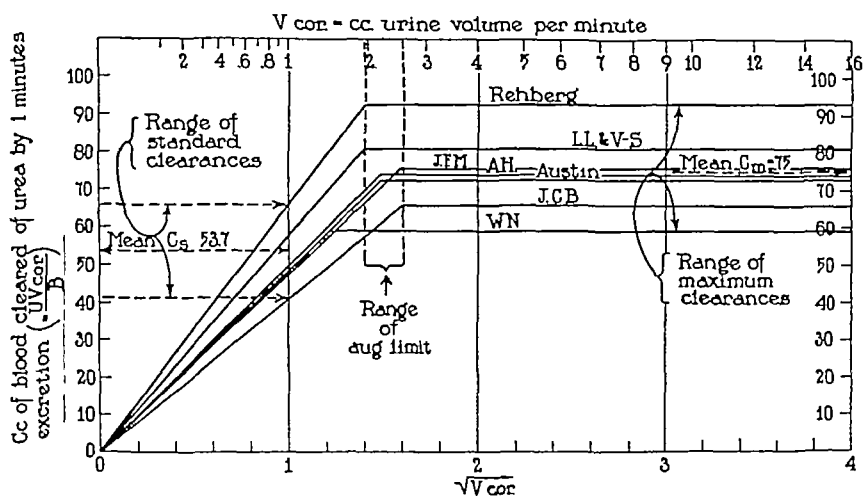


FIG 11

Same curves as in Figure 10, but corrected for body size by multiplying  $V$  values by the correction factor  $\frac{1.73}{\text{square meters surface area}}$

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1 Increase in urine volume diminishes the amount of work the kidney has to do against osmotic pressure in compressing each gram of urea from the volume it occupies in the blood to the smaller volume it occupies in the urine. Less work is required to compress the urea of 100 cc of blood into 2 cc of urine than to compress it further into 1 cc of urine. The kidneys, because they work more easily with increased urine volume, may work faster, and excrete more urea per minute. From this view point, the increase in urea excretion rate which accompanies accelerated water output is a direct cause of the latter. (For quantitative calculation according to the laws of thermodynamics of the mechanical work done by the kidney per gram molecule of substance excreted see pages 93 to 96 of Barcroft (1914))

2 The other hypothesis is that increase of renal circulation, or stimulus of the secretory activity of the renal cells, may accelerate excretion of both urea and water. The accelerated water output in this case would not be the cause of the accelerated urea output. Both would be due to a common stimulus acting on the kidney. Even dilution of the blood by water drinking might be such a cause, either inducing larger proportions of renal capillaries to open up (*vide* Richards (1920-21)) or, making the secretory cells become more active.

For the purpose of estimating from urea excretion the work which the kidneys will do under standard conditions it is, however, a matter of indifference whether the acceleration of urea output that comes with increased urine volume is caused by the latter, or merely accompanies it as the result of a renal stimulus that affects both. Whether, in introducing  $\sqrt{V}$  as a factor in the standard blood urea clearance calculation, we are dealing with the direct cause of fluctuations of clearance with urine volume, or are using urine volume as a fairly consistent indicator of such cause, does not greatly matter when we are concerned merely with measurement of renal ability.

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clearance  $C_s$ , and maximum blood urea clearance  $C_m$ , defined in the preceding paper (6), are accordingly written as

$$C_s = \frac{U}{B} \sqrt{V \times \frac{1.73}{A}} = \frac{U}{B} \sqrt{V_{\text{cor}}}$$

$$C_m = \frac{U}{B} \times V \times \frac{1.73}{A} = \frac{U \times V_{\text{cor}}}{B}$$

The corrected urine volume,  $V_{\text{cor}}$ , is the observed volume of urine in cubic centimeter per minute multiplied by the factor  $\frac{1.73}{A}$ ,  $A$  being the body area in square meters that is normal for the subject's height and age. The clearance formulae, written with  $V_{\text{cor}}$  in place of  $V$ , indicate the cubic centimeters of blood per *unit surface area* cleared of urea per minute, the unit of surface urea being 1.73 square meters. In the case of the  $C_s$  formula, with  $V_{\text{cor}}$ , the value calculated indicates the cubic centimeters blood clearance per unit surface area when the per minute urine volume is 1 cc per unit surface area. Blood clearance, urine volume, and hence augmentation limit are thus all based on surface area. (See derivation of original formula on page 102 of Austin, Stillman and Van Slyke (1))

The *correction for body size* is applied as follows. The age and height of the subject having been ascertained, the value of the correction factor  $\frac{1.73}{A}$  is read from the line chart in figure 1. The observed value of  $V$ , in cubic centimeters of urine per minute, is multiplied by this factor. The corrected  $V$  thus obtained is used in the standard clearance formula,  $C_s = \frac{U \sqrt{V_{\text{cor}}}}{B}$ , or the maximum clearance formula,  $C_m = \frac{UV_{\text{cor}}}{B}$ , for the calculations outlined in the preceding paper (6).

In the correction factor  $\frac{1.73}{A}$ ,  $A$  represents in square meters the mean surface area of normal persons of the subject's height and age. Surface area is thus used as the nearest available parallel to the mass of functioning renal tissue (8) present in a normal subject. Because of the likelihood that the subjects examined will be obese, edematous, or

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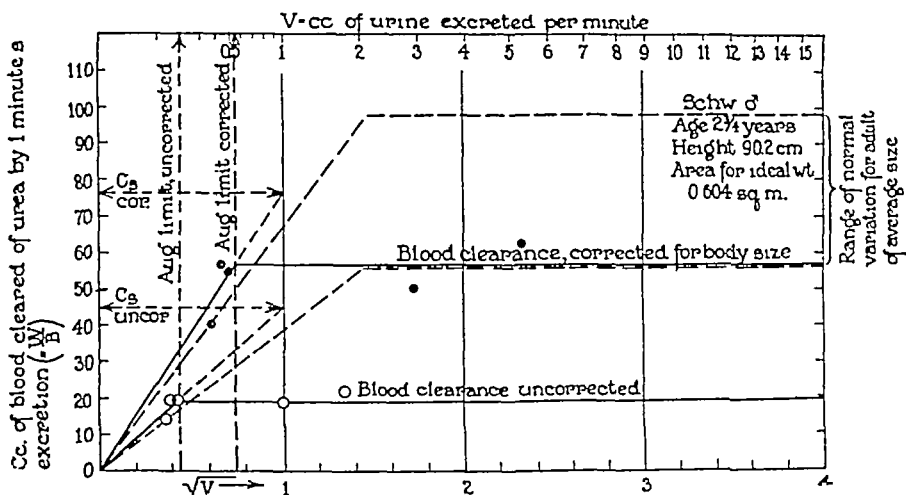


FIG 2 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 13.6 KGM IDEAL WEIGHT

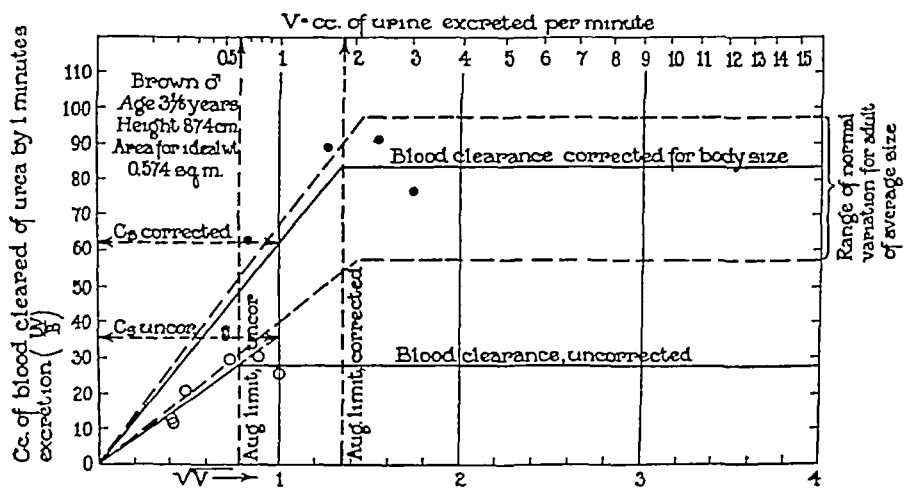


FIG 3 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 12.6 KGM IDEAL WEIGHT

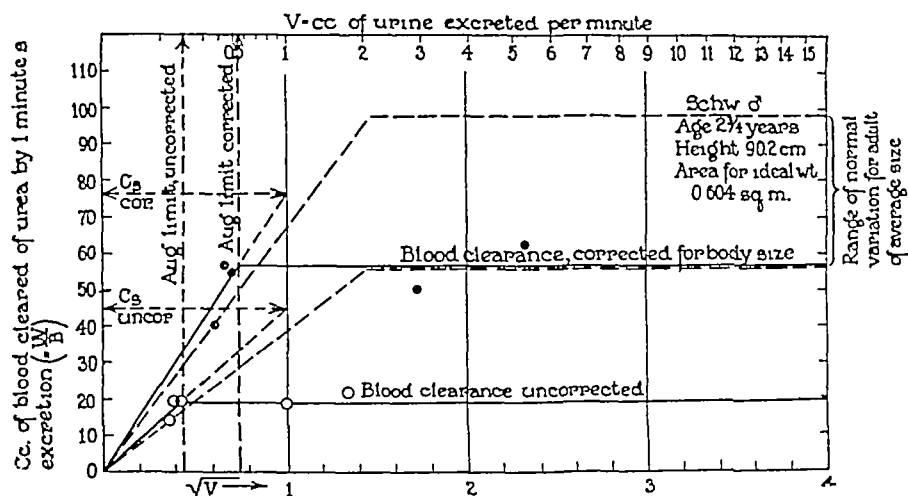


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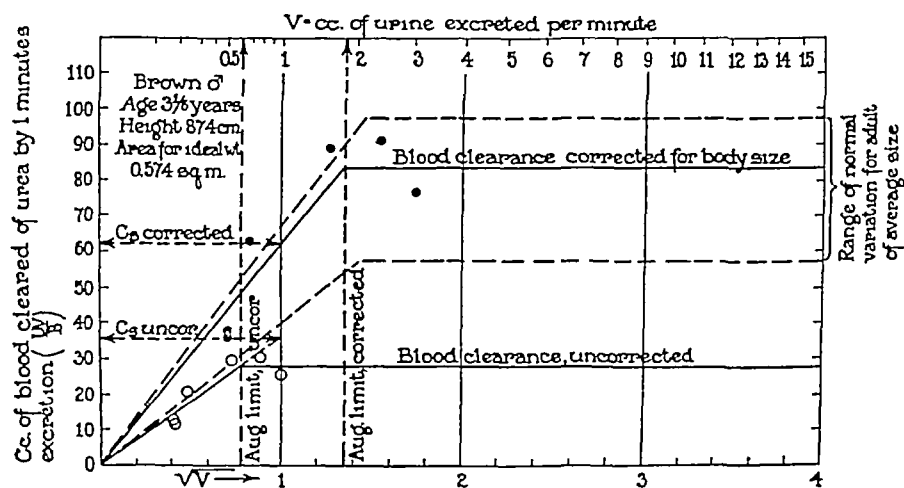


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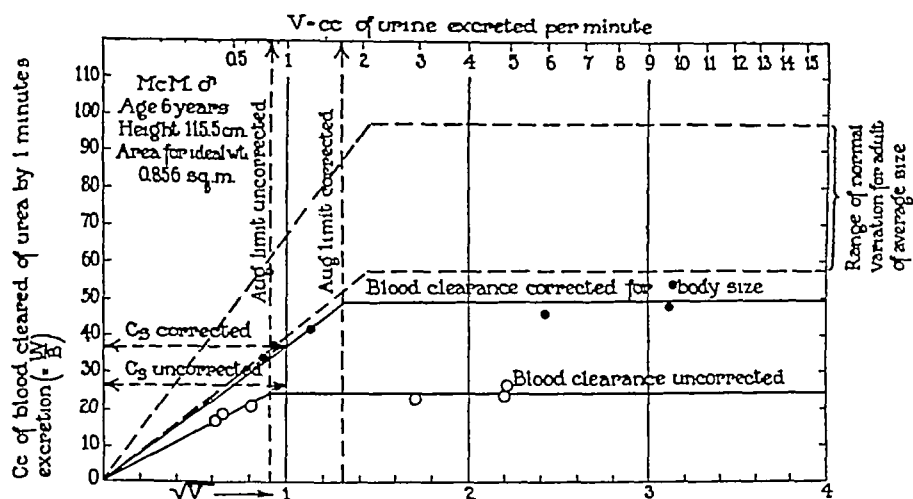


FIG 6 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 21.1 KGM IDEAL WEIGHT

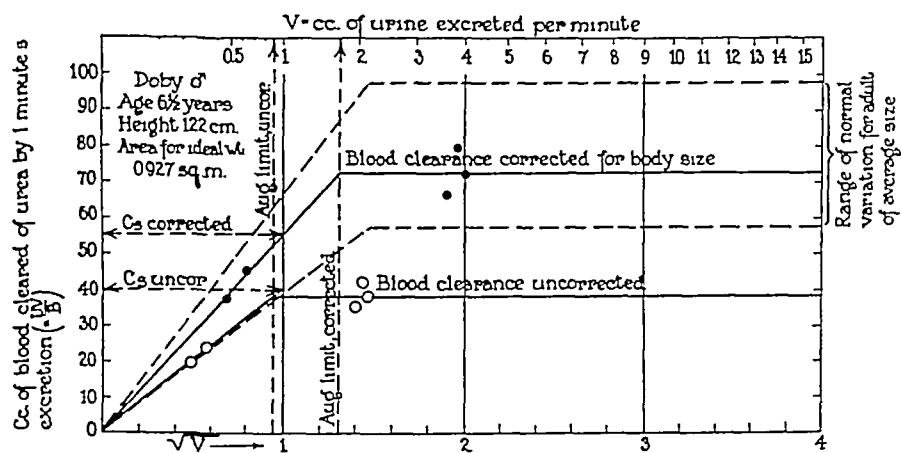


FIG 7 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 23.8 KGM IDEAL WEIGHT

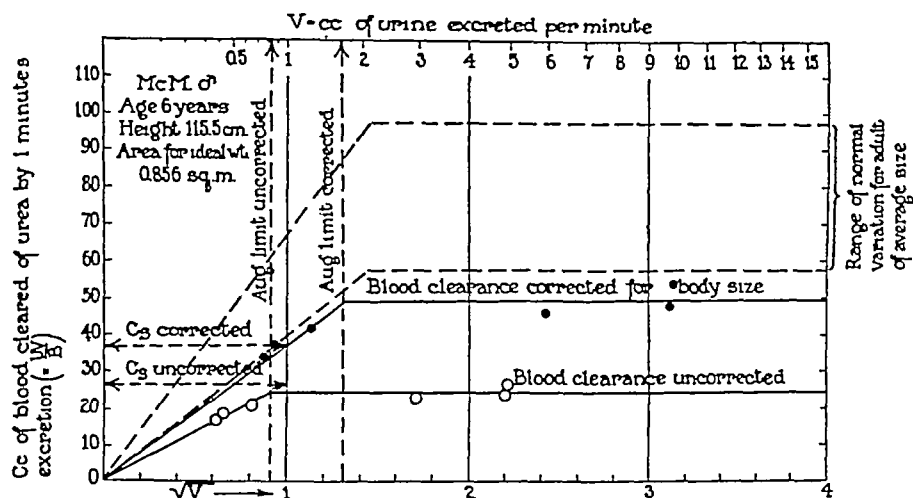


FIG 6 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 21.1 KGM IDEAL WEIGHT

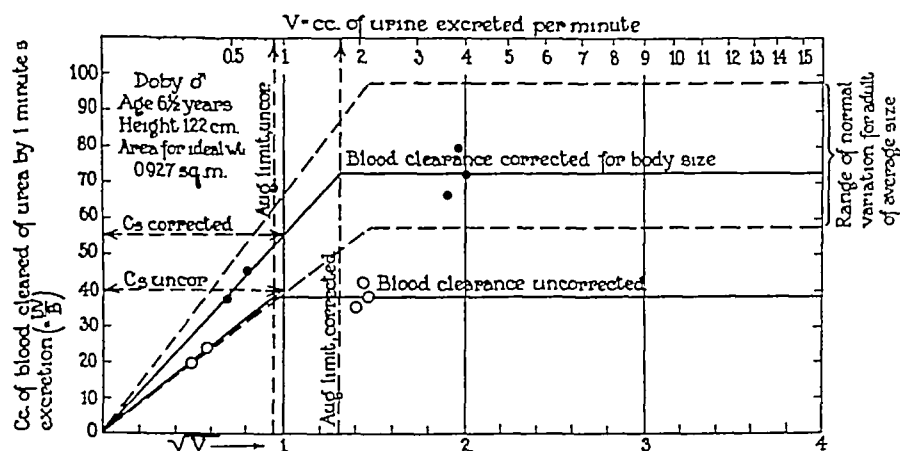


FIG 7 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 23.8 KGM IDEAL WEIGHT



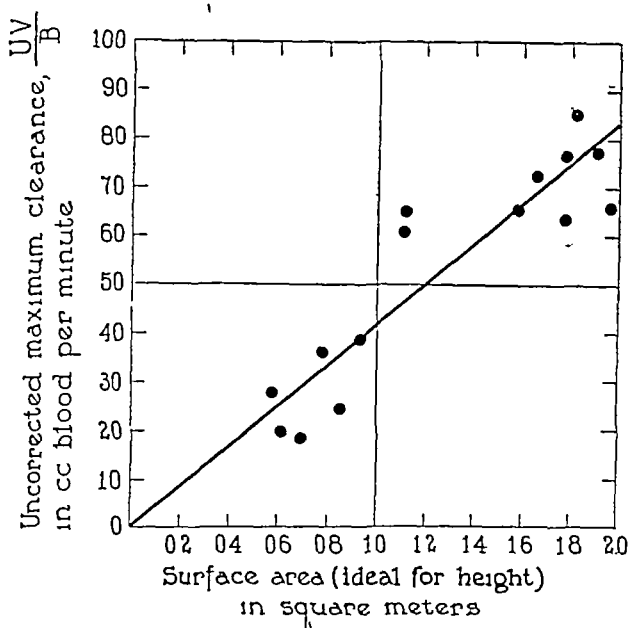


FIG 10 RELATIONSHIP OF SURFACE AREA TO UNCORRECTED MAXIMUM CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

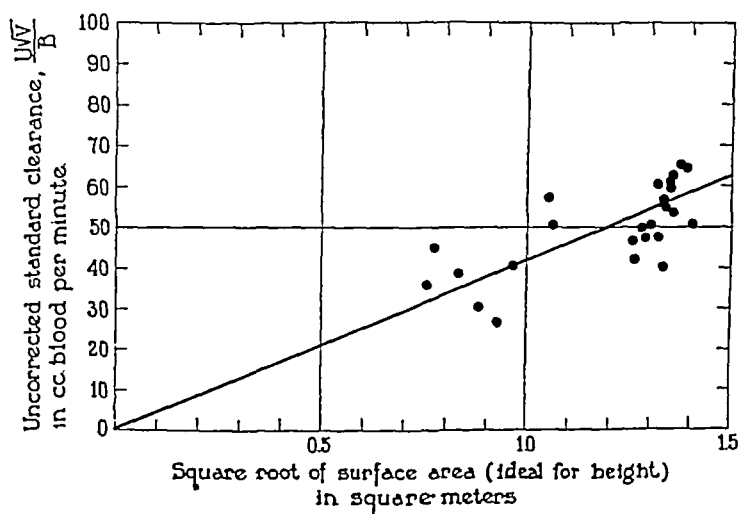


FIG 11 RELATIONSHIP OF SURFACE AREA TO UNCORRECTED STANDARD CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

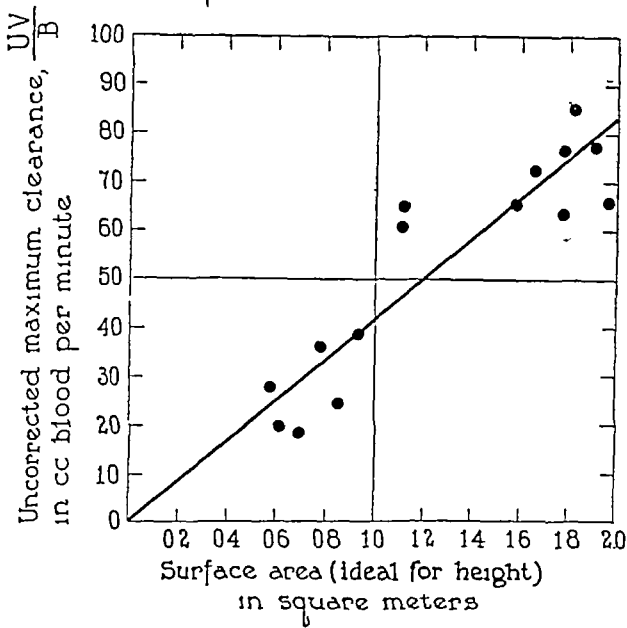


FIG 10 RELATIONSHIP OF SURFACE AREA TO UNCORRECTED MAXIMUM CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

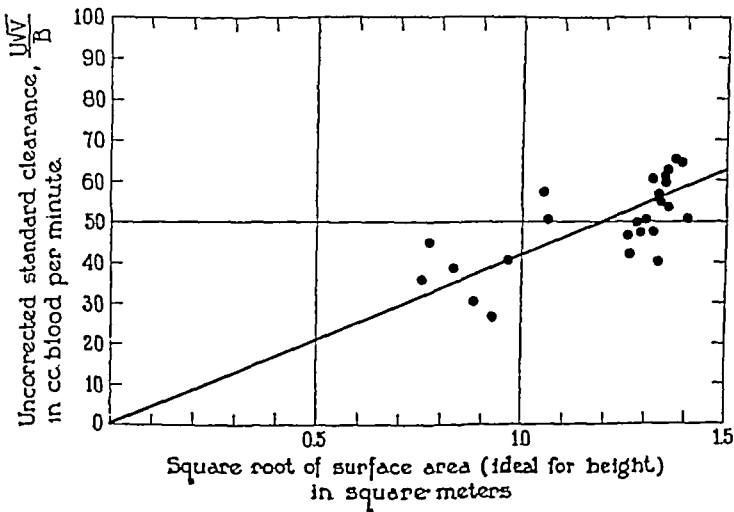


FIG 11 RELATIONSHIP OF SURFACE AREA TO UNCORRECTED STANDARD CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

TABLE 1  
Data concerning urea excretion

| Subject  | U<br>Urine urea<br>nitrogen | B<br>Blood urea<br>nitrogen | V<br>Urine<br>volume | $V \times \frac{1.73}{\text{Area}}$<br>Urine volume<br>corrected<br>for body size | Uncorrected clearances                   |   | Clearances corrected for body size                                |  |
|--|-----------------------------|-----------------------------|----------------------|---|--|---|---|--|
|  |                             |                             |                      |   | $\frac{UV}{B}$<br>Observed<br>clearance* | $\frac{U\sqrt{V}}{B}$<br>Standard clear<br>ance calculated for<br>$V = 1$ from<br>observations<br>below augmenta-<br>tion limit | $\frac{U(V \times \frac{1.73}{A})}{B}$<br>Observed clear<br>ance* | $\frac{U\sqrt{V \times \frac{1.73}{A}}}{B}$<br>Standard clearance<br>calculated for<br>$V \times \frac{1.73}{A} = 1$<br>from observations<br>below augmenta-<br>tion limit |
| Schw $\sigma^7$<br>2 $\frac{6}{12}$ years<br>159 kgm<br>90.2 cm height<br>0.620 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 2.80$ | mgm per<br>100 cc           | mgm per<br>100 cc           | cc per<br>minute     | cc per minute   | cc blood<br>per minute                   | cc blood per minute   | cc blood per minute   | cc blood per minute  |
|  | 1,121                       | (10.5)                      | 0.132                | 0.370   | 14.1                                     | 38.8  | 39.5  | 64.9   |
|  | 1,346                       | 10.5                        | 0.154                | 0.431   | 19.8                                     | 50.4  | 55.3  | 84.2   |
|  | 1,147                       | 10.5                        | 0.176                | 0.493   | 19.2                                     | 45.8  | 53.8  | 76.5   |
|  | 260                         | 15.1                        | 1.03                 | 0.287   | 17.7*                                    |   | 49.4*   |  |
|  | 175                         | (15.0)                      | 1.88                 | 0.529   | 21.9*                                    |   | 61.7*   |  |
| Average clearance  |                             |                             |                      |   | 19.8*                                    | 45.0  | 55.5*   | 75.2   |
| Brown $\sigma^7$<br>3 $\frac{1}{2}$ years<br>116 kgm<br>87.1 cm height<br>0.595 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 2.91$ | 832                         | 11.0                        | 0.167                | 0.486   | 12.6                                     | 30.9  | 36.7  | 52.6   |
|  | 756                         | (10.6)                      | 0.167                | 0.486   | 11.9                                     | 29.2  | 34.7  | 49.7   |
|  | 912                         | 10.2                        | 0.233                | 0.677   | 20.8                                     | 43.2  | 60.6  | 73.5   |
|  | 527                         | 9.5                         | 0.534                | 1.55  | 29.5                                     | 40.4  | 86.0  | 69.0   |
|  | 337                         | 8.9                         | 0.793                | 2.4   | 30.2*                                    |   | 90.8*   |  |
|  | 235                         | (9.20)                      | 1.000                | 2.91  | 25.5*                                    |   | 74.4*   |  |
| Average clearance  |                             |                             |                      |   | 27.9*                                    | 35.9  | 82.6*   | 61.2   |

TABLE 1

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| Subject   | U<br>Urine urea<br>nitrogen | B<br>Blood urea<br>nitrogen | V<br>Urine<br>volume | $V \times \frac{1.73}{\text{Area}}$<br>Urine volume<br>corrected<br>for body size | Uncorrected clearances                   |   | Clearances corrected for body size                                |  |
|---|-----------------------------|-----------------------------|----------------------|---|--|---|---|--|
|   |                             |                             |                      |   | $\frac{UV}{B}$<br>Observed<br>clearance* | $\frac{U\sqrt{V}}{B}$<br>Standard clear<br>ance calculated for<br>$V = 1$ from<br>observations<br>below augmenta-<br>tion limit | $\frac{U(V \times \frac{1.73}{A})}{B}$<br>Observed clear<br>ance* | $\frac{U\sqrt{V \times \frac{1.73}{A}}}{B}$<br>Standard clearance<br>calculated for<br>$V \times \frac{1.73}{A} = 1$<br>from observations<br>below augmenta-<br>tion limit |
| Schw $\sigma$<br>2 $\frac{1}{2}$ years<br>15.9 kgm<br>90.2 cm height<br>0.620 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 2.80$  | mgm per<br>100 cc           | mgm per<br>100 cc           | cc per<br>minute     | cc per minute   | cc blood<br>per minute                   | cc blood per minute   | cc blood per minute   | cc blood per minute  |
|   | 1,121                       | (10.5)                      | 0.132                | 0.370   | 14.1                                     | 38.8  | 39.5  | 64.9   |
|   | 1,346                       | 10.5                        | 0.154                | 0.431   | 19.8                                     | 50.4  | 55.3  | 84.2   |
|   | 1,147                       | 10.5                        | 0.176                | 0.493   | 19.2                                     | 45.8  | 53.8  | 76.5   |
|   | 260                         | 15.1                        | 1.03                 | 0.287   | 17.7*                                    |   | 49.4*   |  |
|   | 175                         | (15.0)                      | 1.88                 | 0.529   | 21.9*                                    |   | 61.7*   |  |
| Average clearance   |                             |                             |                      |   | 19.8*                                    | 45.0  | 55.5*   | 75.2   |
| Brown $\sigma$<br>3 $\frac{1}{2}$ years<br>11.6 kgm<br>87.4 cm height<br>0.505 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 2.91$ | 832                         | 11.0                        | 0.167                | 0.486   | 12.6                                     | 30.9  | 36.7  | 52.6   |
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|   | 912                         | 10.2                        | 0.233                | 0.677   | 20.8                                     | 43.2  | 60.6  | 73.5   |
|   | 527                         | 9.5                         | 0.534                | 1.55  | 29.5                                     | 40.4  | 86.0  | 69.0   |
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|   | 235                         | (9.20)                      | 1.000                | 2.91  | 25.5*                                    |   | 74.4*   |  |
| Average clearance   |                             |                             |                      |   | 27.9*                                    | 35.9  | 82.6*   | 61.2   |

TABLE 1—Continued

| Subject  | U<br>Urine urea<br>nitrogen<br>mgm per<br>100 cc | B<br>Blood urea<br>nitrogen<br>mgm per<br>100 cc | V<br>Urine<br>volume<br>cc per<br>minute | $V \times \frac{1.73}{\text{Area}}$<br>Urine volume<br>corrected<br>for body size<br>cc per minute | Uncorrected clearances                   |  | Clearances corrected for body size                                    |   |
|--|--|--|--|--|--|--|---|---|
|  |  |  |  |  | $\frac{UV}{B}$<br>Observed<br>clearance* | $\frac{U \sqrt{V}}{B}$<br>Standard clear<br>ance calculated for<br>$V = 1$ from<br>observations<br>below augmenta<br>tion limit<br>cc blood per minute | $U \left( \frac{V \times 1.73}{B} \right)$<br>Observed clear<br>ance* | $\frac{U \sqrt{V \times \frac{1.73}{A}}}{B}$<br>Standard clearance<br>calculated for<br>$V \times \frac{1.73}{A} = 1$<br>from observations<br>below augmenta<br>tion limit<br>cc blood per minute |
| Doly ♂<br>6 $\frac{1}{2}$ years<br>21.3 kgm<br>122.0 cm height<br>0.927 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 1.87$ | 1,435  | 18.0   | 0.250                                    | 0.467  | 19.9                                     | 39.9   | 37.2  | 54.5  |
|  | 1,270  | 17.9   | 0.343                                    | 0.640  | 24.3                                     | 41.6   | 45.4  | 56.8  |
|  | 307  | 17.0   | 1.97                                     | 3.68   | 35.6*                                    |  | 66.5*   |   |
|  | 281  | 13.8   | 2.08                                     | 3.88   | 42.4*                                    |  | 79.2*   |   |
|  | 303  | 17.0   | 2.17                                     | 4.05   | 38.7*                                    |  | 72.3*   |   |
|  | Average clearance                                |  |  |  | 38.9*                                    | 40.8   | 72.7*   | 55.7  |
| Gann ♀<br>9 years<br>26.8 kgm<br>137 cm height.<br>1.12 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 1.55$                 | 937  | (13.2)   | 0.486                                    | 0.751  | 34.5                                     | 49.5   | 53.3  | 61.6  |
|  | 1,115  | 13.2   | 0.548                                    | 0.846  | 46.3                                     | 62.6   | 71.5  | 77.8  |
|  | 653  | 11.7   | 0.594                                    | 0.918  | 33.2                                     | 43.0   | 51.3  | 53.5  |
|  | 466  | 9.4  | 0.833                                    | 1.29   | 41.3                                     | 45.2   | 63.8  | 56.2  |
|  | 488  | 8.2  | 0.933                                    | 1.44   | 55.5                                     | 57.5   | 85.8  | 71.5  |
|  | 453  | 8.8  | 1.07                                     | 1.65   | 54.9                                     | 53.2   | 84.8  | 66.2  |
|  | 435  | 9.2  | 1.07                                     | 1.65   | 50.4                                     | 48.9   | 77.8  | 60.8  |
|  | 479  | 11.9   | 1.08                                     | 1.67   | 43.6                                     | 41.8   | 67.4  | 52.0  |
|  | 273  | 14.0   | 3.40                                     | 5.25   | 66.3*                                    |  | 102.5*  |   |
|  | 197  | 14.5   | 4.69                                     | 7.24   | 63.8*                                    |  | 98.6*   |   |
|  | Average clearance.                               |  |  |  | 65.1*                                    | 50.2   | 100.6*  | 62.5  |

TABLE 1—Continued

| Subject  | U<br>Urine urea<br>nitrogen<br>mgm per<br>100 cc | B<br>Blood urea<br>nitrogen<br>mgm per<br>100 cc | V<br>Urine<br>volume<br>cc per<br>minute | $V \times \frac{1.73}{\text{Area}}$<br>Urine volume<br>corrected<br>for body size<br>cc per minute | Uncorrected clearances                   |   | Clearances corrected for body size  |   |
|--|--|--|--|--|--|---|---|---|
|  |  |  |  |  | $\frac{UV}{B}$<br>Observed<br>clearance* | $\frac{U \sqrt{V}}{B}$<br>Standard clear<br>ance calculated for<br>$V = 1$ from<br>observations<br>below augmenta<br>tion limit | $U \left( V \times \frac{1.73}{A} \right) / B$<br>Observed clear<br>ance* | $U \sqrt{\frac{1.73}{V \times \frac{1.73}{A}}}$<br>Standard clearance<br>calculated for<br>$V \times \frac{1.73}{A} = 1$<br>from observations<br>below augmenta<br>tion limit |
| Doty ♂<br>6 $\frac{1}{2}$ years<br>21.3 kgm<br>122.0 cm height<br>0.927 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 1.87$ |  |  |  |  | cc blood per minute                      | cc blood per minute   | cc blood per minute   | cc blood per minute   |
|  | 1,435  | 18.0   | 0.250                                    | 0.467  | 19.9                                     | 39.9  | 37.2  | 54.5  |
|  | 1,270  | 17.9   | 0.343                                    | 0.640  | 24.3                                     | 41.6  | 45.4  | 56.8  |
|  | 307  | 17.0   | 1.97                                     | 3.68   | 35.6*                                    |   | 66.5*   |   |
|  | 281  | 13.8   | 2.08                                     | 3.88   | 42.4*                                    |   | 79.2*   |   |
|  | 303  | 17.0   | 2.17                                     | 4.05   | 38.7*                                    |   | 72.3*   |   |
| Average clearance  |  |  |  |  | 38.9*                                    | 40.8  | 72.7*   | 55.7  |
| Gann ♀<br>9 years<br>26.8 kgm<br>137 cm height.<br>1.12 sq m surface area<br>ideal for height<br>$\frac{1.73}{\text{Area}} = 1.55$                 |  |  |  |  |  |   |   |   |
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| Average clearance.   |  |  |  |  | 65.1*                                    | 50.2  | 100.6*  | 62.5  |

In estimating the maximum blood urea clearance, however, by the formula  $C_m = \frac{UV}{B}$ , a 10 per cent correction to  $V$  causes a 10 per cent correction to the  $C_m$  value calculated. Hence, to avoid an error greater than  $\pm 5$  per cent, we can neglect body size in estimating the maximum clearance only in adults between 164 and 176 cm, or 65 and 69 inches, in height.

#### EXPERIMENTAL

In order to measure satisfactorily the influence of body size on urea excretion rate it is necessary to compare children with adults. With ordinary adults variation in size, as a factor in influencing the volume of blood, the urea content of which is excreted per minute, is less important than other, unknown factors, which may be summarized as "individual constitution." These may cause the standard or maximum clearance of an individual, of average size and normal to all appearances, to vary by as much as 25 per cent from the mean normal clearance. The effect of body size is so obscured by the greater effects of individual constitution that the size effect in adults can be measured only by statistical methods. In order to make it an outstanding factor it is necessary to study subjects with a greater size range than can be obtained in the adults usually available for observation.

We have accordingly, by the technique described in the preceding paper (6), determined the urea excretion curves on a number of children. The numerical data are given in table 1, and the curves in figures 2 to 9. The correction for body size is made, as previously described, by multiplying the observed  $V$  value by the factor  $\frac{1.73}{A}$ .

#### DISCUSSION OF RESULTS

It is obvious from figures 2, 3, 4, 5, 6, 7, 8, and 9, that correcting the blood urea clearances, by multiplying the observed values of  $V$  in cc urine excreted per minute by the factor  $\frac{\text{average adult surface area}}{\text{surface area of subject}} = \frac{1.73}{A}$ , causes data from children, at least down to 3 years of age, to fall

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jects do not decrease so rapidly as body weights. They decrease rather as the surface area, or the  $2/3$  power of the weight

The degree of exactness with which the maximum clearance,  $\frac{UV}{B}$ , varies in proportion to surface area in different subjects is indicated by figure 10 in which we have plotted against surface area the mean maximum clearance for each of the 7 adults reported from this laboratory in the preceding paper (6), and each of the children reported in the present paper. In figure 11 the uncorrected standard clearance,  $\frac{U\sqrt{V}}{B}$ , is similarly plotted against the square root of surface area for each of the 17 adults reported in the preceding paper, and each of the children in the present one

#### SUMMARY

The calculated maximum and standard blood urea clearances, previously defined (6), may be corrected for variations in body size by means of a factor based on the assumption, introduced by Addis (8), that excretion varies directly as surface area. Thus corrected, data from small children yield the same normal values as adults for the maximum and standard clearances, and also for the augmentation limit of urine volume, at which maximum excretory efficiency is attained.

The nature of the standard clearance formula is such that correction for body size in persons between 62 and 71 inches in height does not exceed 5 per cent, and in tests of renal function may be neglected.

For the maximum clearance the range of height with less than 5 per cent correction is 65 to 69 inches.

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- 1 Austin, J. H., Stillman, E., and Van Slyke, D. D., *J. Biol. Chem.*, 1921, **xli**, 91. Factors Governing the Excretion Rate of Urea.
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TABLE 1  
Data of cases

| Case                             | Blood pressure | Size of heart          | Eye grounds | Hemoglobin as O <sub>2</sub> capacity | Red blood corpuscles<br>mil<br>lions<br>per<br>cu<br>mm | White blood corpuscles<br>per<br>cu<br>mm | Plasma proteins |          |               |           | Blood urea<br>mgm<br>per<br>100<br>cc | Plasma creatinine<br>mgm<br>per<br>100<br>cc | Plasma non protein N<br>mgm<br>per<br>100<br>cc | Urine protein (Esbach)<br>grams<br>per<br>liter | Diuresis (ca)<br>cc | Specific gravity | Sediment   | Phenolsulfonphthalein test in<br>two hours<br>per<br>cent | Mean standard blood<br>$\frac{U}{V}$ urea,<br>clearance corrected to body size |
|----------------------------------|----------------|------------------------|-------------|---------------------------------------|---|---|-----------------|----------|---------------|-----------|---------------------------------------|--|---|---|---------------------|------------------|--|---|--|
|                                  |                |                        |             |                                       |   |   | Albumin         | Globulin | Total protein | A/G ratio |                                       |  |   |   |                     |                  |  |   |  |
| 1<br>Chi<br>Hospital<br>No 5335  | 100/70         | Normal                 | Nor<br>mal  | 13 2<br>vol<br>umes<br>per<br>cent    | 4 98 5<br>per<br>cu<br>mm                               | 500 3                                     | 34 2            | 32 5     | 66 1          | 44        | 15                                    | 1 3  | 34  | 0 3   | 1 000               | 1013-<br>1017    | +++ RBC, + hyaline and<br>granular casts, no DRG*                | 70  | 62   |
| 2<br>Jac.<br>Hospital<br>No 5699 | 134/85         | Slightly in<br>creased | Nor<br>mal  | 20 2                                  | 5 31 6  | 100 1                                     | 71 2            | 11 3     | 82 0          | 81        | 20                                    | 1 9  | 41  | 4   | 1 000               | 1012-<br>1018    | + RBC, + WBC, +++<br>hyaline casts, +- granu<br>lar casts, + DRG | 22  | 22   |
| 3<br>C.C.<br>Hospital<br>No 5644 | 115/80         | Normal                 | Nor<br>mal  | 20 1                                  | 4 50 8  | 900 1                                     | 70 2            | 24 3     | 94 0          | 76        | 22                                    | 1 9  | 29  | 6   | 1 200               | 1010-<br>1014    | + RBC, + WBC, +++<br>hyaline casts, + granu<br>lar casts, + DRG  | 35  | 18   |
| 4<br>Val<br>Hospital<br>No 5446  | 145/75         | Somewhat<br>increased  | Nor<br>mal  | 12 0                                  | 4 39 7  | 300 2                                     | 11 1            | 92 4     | 03 1          | 10        | 40                                    | 3 0  | 32  | 6   | 1 600               | 1010-<br>1018    | +++ RBC, ++ WBC, ++<br>RBC casts, +- granular<br>casts, no DRG   |   |  |

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|-----------------------------|----------------|------------------------|-------------|---------------------------------------|---|---|------------------------|-------------------------|------------------------------|-----------|---------------------------------------|--|---|---|---------------------|------------------|--|--|---|
|                             |                |                        |             |                                       |   |   | Albumin<br>per<br>cent | Globulin<br>per<br>cent | Total protein<br>per<br>cent | A/G ratio |                                       |  |   |   |                     |                  |  |  |   |
| Chi<br>Hospital<br>No 5335  | 100/70         | Normal                 | Nor<br>mal  | 13 2                                  | 4 98  | 5 500                                     | 3 34                   | 2 32                    | 5 66                         | 1 44      | 15                                    | 1 3  | 34  | 0 3   | 1 000               | 1013-<br>1017    | +++ RBC, + hyaline and<br>granular casts, no DRG*                | 70   | 62  |
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| Cic.<br>Hospital<br>No 5644 | 115/80         | Normal                 | Nor<br>mal  | 20 1                                  | 4 50  | 8 900                                     | 1 70                   | 2 24                    | 3 94                         | 0 76      | 22                                    | 1 9  | 29  | 6   | 1 200               | 1010-<br>1014    | + RBC, + WBC, +++<br>hyaline casts, + granu<br>lar casts, + DRG  | 35   | 18  |
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The laboratory findings in our 6 cases of Bright's disease are given in table 1. The terms of classification are those used by Addis (1).

#### CASE HISTORIES

*Case 1 Chi* Hospital No 5335 Boy, 13 years old. When 7 years old he had acute glomerulonephritis, now relapse with hematuria and some edema.

TABLE 2  
*Correction factors for body size*

| Case |        |                 | Age   | Weight | Height | Body surface area observed | Weight ideal for height and age | Area ideal for height and age | Correction factor                   |                                  |
|------|--------|-----------------|-------|--------|--------|----------------------------|---------------------------------|-------------------------------|-------------------------------------|----------------------------------|
| Name | Number | Hospital number |       |        |        |                            |                                 |                               | $\frac{1.73}{\text{Area observed}}$ | $\frac{1.73}{\text{Area ideal}}$ |
|      |        |                 | years | kgm    | cm     | sq m                       | kgm                             | sq m                          |                                     |                                  |
| Chi  | 1      | 5335            | 13    | 38     | 145.9  | 1.30*                      | 37.5                            | 1.29*                         | 1.33                                | 1.34                             |
| Jas  | 2      | 5699            | 24    | 56     | 173.0  | 1.66                       | 66.8                            | 1.79                          | 1.04                                | 0.97                             |
| Cic  | 3      | 5644            | 24    | 48     | 163.4  | 1.50                       | 59.8                            | 1.65                          | 1.15                                | 1.05                             |
| Val  | 4      | 5446            | 24    | 59     | 176.0  | 1.73                       | 69.2                            | 1.84                          | 1.00                                | 0.94                             |
| Gia  | 5      | 5388            | 24    | 64     | 175.0  | 1.79                       | 68.3                            | 1.83                          | 0.97                                | 0.95                             |
| Wol  | 6      | 5731            | 16    | 38     | 155.0  | 1.31                       | 46.9                            | 1.43                          | 1.32                                | 1.21                             |

\* Calculated from the table of Benedict and Talbot for children. Carnegie Trust Wash. Publ. No. 302, 1921, p. 61.

Surface areas of other patients are calculated by Du Bois' formula.

No loss of ability to excrete urea or phthalein. *Course of the disease.* After 6 weeks sent home with no edema, only a trace of albuminuria, and a slight microscopic hematuria. Seen 6 months and one year later, when the hematuria had quite disappeared, while the slight albuminuria persisted. Other findings normal.

*Case 2 Jac* Hospital No 5699 Man, 24 years old. One year ago, tonsillitis followed by albuminuria and marked edema. This cleared up gradually in 6 months, but after chrysarobin treatment for psoriasis severe relapse set in with edema, ascites and hydrothorax. *Course of the disease.* Edema and anasarca cleared up completely in one month. Seen 6 months later, there was then no edema and only a few red cells and casts in the urine.

*Case 3 Cic* Hospital No 5644 Man, 24 years old. Syphilis found 6 years ago, since then repeated treatment with salvarsan and mercury. One

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| Gia  | 5      | 5388            | 24    | 64     | 175.0  | 1.79                       | 68.3                            | 1.83                          | 0.97                                | 0.95                             |
| Wol  | 6      | 5731            | 16    | 38     | 155.0  | 1.31                       | 46.9                            | 1.43                          | 1.32                                | 1.21                             |

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TABLE 3  
Data concerning urea excretion

|   | Time                   | V<br>Urine<br>volume | V cor<br>Urine volume<br>corrected for body<br>size by factor<br>$\frac{1.73}{\text{Area}}$ from table 2 | U<br>Urine urea<br>nitrogen | B<br>Blood urea<br>nitrogen | $\frac{UV \text{ cor}}{B}$<br>Observed<br>clearance* | $\frac{U \sqrt{V \text{ cor}}}{B}$<br>Calculated stand-<br>ard and below<br>augmentation<br>limit | Per cent<br>of average<br>normal<br>clearance |
|---|------------------------|----------------------|--|-----------------------------|-----------------------------|--|---|---|
|   |                        | cc per<br>minute     | cc per minute  | mgm<br>per 100 cc           | mgm<br>per 100 cc           | cc blood<br>per minute                               | cc blood per<br>minute  | per cent                                      |
| Exp No A 12 Chi<br>8 50 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 97                 | 1 30   | 413                         | 7 5                         | 71 6   | 62 7  | 116   |
| Exp No A 13 Chi<br>8 40 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 67                 | 0 90   | 678                         | 10 1                        | 60 0   | 63 6  | 118   |
| Exp No A 14 Chi<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 41                 | 0 55   | 1019                        | 11 9                        | 96 9   | 63 4  | 117   |
| Exp No A 15 Chi<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 21                 | 0 28   | 966                         | 11 1                        | 24 4   | 46 2  | 85  |
| Exp No A 16 Chi<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 30                 | 0 40   | 828                         | 7 0                         | 47 6   | 75 0  | 139   |
| Exp No A 17 Chi<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 28                 | 0 38   | 1005                        | 10 1                        | 37 4   | 61 0  | 113   |
| Exp No A 18 Chi<br>6 a m, 20 grms urea and 300 cc of<br>water 7, 8, 9, 10, and 11 a m, 300<br>cc of water each time. Venous blood | 9-10<br>10-11<br>11-12 | 6 50<br>6 92<br>4 50 | 8 71<br>9 27<br>6 03   | 282<br>240<br>336           | 30 4<br>27 0<br>25 1        | 80 9*<br>82 4*<br>80 7*                              | 61 0  | 108*<br>110*<br>108*                          |

TABLE 3  
Data concerning urea excretion

|  | Time                   | V<br>Urine<br>volume | V cor<br>Urine volume<br>corrected for body<br>size by factor<br>$\frac{1.73}{\text{Area}}$ from table 2 | U<br>Urine urea<br>nitrogen | B<br>Blood urea<br>nitrogen | $\frac{UV \text{ cor}}{B}$<br>Observed<br>clearance* | $\frac{U \sqrt{V \text{ cor}}}{B}$<br>Calculated stand<br>ard below<br>clearance (for V)<br>augmentation<br>limit | Per cent<br>of average<br>normal<br>clearance |
|--|------------------------|----------------------|--|-----------------------------|-----------------------------|--|---|---|
|  |                        | cc per<br>minute     | cc per minute  | mgm<br>per 100 cc           | mgm<br>per 100 cc           | cc blood<br>per minute                               | cc blood per<br>minute  | per cent                                      |
| Exp No A 12 Chl<br>8 50 a m, 100 cc of water<br>blood Venous   | 9-11                   | 0 97                 | 1 30   | 413                         | 7 5                         | 71 6   | 62 7  | 116   |
| Exp No A 13 Chl<br>8 40 a m, 100 cc of water<br>blood Venous   | 9-11                   | 0 67                 | 0 90   | 678                         | 10 1                        | 60 0   | 63 6  | 118   |
| Exp No A 14 Chl<br>8 20 a m, 100 cc of water<br>blood Venous   | 9-11                   | 0 41                 | 0 55   | 1019                        | 11 9                        | 96 9   | 63 4  | 117   |
| Exp No A 15 Chl<br>8 20 a m, 100 cc of water<br>blood Venous   | 9-11                   | 0 21                 | 0 28   | 966                         | 11 1                        | 24 4   | 46 2  | 85  |
| Exp No A 16 Chl<br>8 20 a m, 100 cc of water<br>blood Venous   | 9-11                   | 0 30                 | 0 40   | 828                         | 7 0                         | 47 6   | 75 0  | 139   |
| Exp No A 17 Chl<br>8 20 a m, 100 cc of water<br>blood Venous   | 9-11                   | 0 28                 | 0 38   | 1005                        | 10 1                        | 37 4   | 61 0  | 113   |
| Exp No A 18 Chl<br>6 a m, 20 grams urea and 300 cc of<br>water 7, 8, 9, 10, and 11 a m, 300<br>cc of water each time. Venous blood | 9-10<br>10-11<br>11-12 | 6 50<br>6 92<br>4 50 | 8 71<br>9 27<br>6 03   | 282<br>240<br>336           | 30 4<br>27 0<br>25 1        | 80 9*<br>82 4*<br>80 7*                              |   | 108*<br>110*<br>108*                          |

TABLE 3—Continued

|  | Time  | V<br>Urine<br>volume | V cor<br>Urine volume<br>corrected for body<br>size by factor<br>$\frac{1.73}{\text{Area}}$ from table 2 | U<br>Urine urea<br>nitrogen | B<br>Blood urea<br>nitrogen | UV cor<br>Observed<br>clearance* | $\frac{U\sqrt{V} \text{ cor}}{B}$<br>Calculated stand<br>ard below<br>clearance (for V)<br>augmentation<br>limit | Per cent<br>of average<br>normal<br>clearance |
|--|-------|----------------------|--|-----------------------------|-----------------------------|----------------------------------|--|---|
|  |       | cc per<br>minute     | cc per minute  | mgm<br>per 100 cc           | mgm<br>per 100 cc           | cc blood<br>per minute           | cc blood per<br>minute   | per cent                                      |
| Exp 20-a Cic<br>9 a m, 100 cc of water<br>Lxp 20 b Cic<br>9 a m, 100 cc of water<br>Lxp 20 c Cic<br>9 a m, 100 cc of water<br>Lxp No 22 Cic<br>7 30 a m, breakfast with 15 grams urea<br>and 1000 cc of water 11 50 a m,<br>lunch with 1000 cc of water 1 20<br>and 2 05 p m, 500 cc of water each<br>time Cutaneous blood | 10-11 | 0 37                 | 0 39   | 384                         | 16 2                        | 9 1                              | 14 8   | 27  |
|  | 11-12 | 0 60                 | 0 63   | 386                         |                             | 15 0                             | 19 0   | 35  |
|  | 10-11 | 0 50                 | 0 53   | 347                         | 15 2                        | 11 9                             | 16 6   | 31  |
|  | 11-12 | 0 35                 | 0 37   | 270                         |                             | 6 6                              | 10 8   | 20  |
|  | 10-11 | 1 27                 | 1 33   | 198                         | 12 1                        | 21 7                             | 18 9   | 35  |
|  | 11-12 | 0 92                 | 0 97   | 299                         |                             | 23 8                             | 24 3   | 45  |
|  | 9-10  | 1 92                 | 2 02   | 354                         | 36 6                        | 19 4*                            |  | 26*   |
|  | 10-11 | 1 87                 | 1 96   | 344                         | 35 1                        | 19 2*                            |  | 26*   |
|  | 11-12 | 1 83                 | 1 92   | 345                         | 34 5                        | 19 2*                            |  | 26*   |
|  | 12-1  | 2 17                 | 2 28   | 349                         | 34 6                        | 22 9*                            |  | 31*   |
|  | 1-2   | 4 17                 | 4 38   | 209                         | 37 0                        | 24 7*                            |  | 33*   |
|  | 2-3   | 4 50                 | 4 73   | 230                         | 35 4                        | 30 7*                            |  | 41*   |
|  | 3-4   | 4 83                 | 5 07   | 185                         | 33 8                        | 27 8*                            |  | 37*   |
| Exp No 14 Val<br>8 a m, breakfast with 100 cc of water<br>12 noon lunch with 1000 cc of water<br>1 40 p m, 500 cc of water Cutane-<br>ous blood<br>Exp No 14-a Val<br>9 a m, 100 cc. of water Venous blood   | 9-10  | 1 10                 | 1 03   | 244                         | 21 8                        | 11 6                             | 11 3   | 21  |
|  | 10-11 | 0 97                 | 0 91   | 265                         | 19 4                        | 12 4                             | 13 1   | 24  |
|  | 11-12 | 0 90                 | 0 85   | 285                         | 18 9                        | 12 9                             | 13 9   | 25  |
|  | 12-1  | 2 17                 | 2 04   | 135                         | 22 1                        | 12 5*                            |  | 17*   |
|  | 1-2   | 5 08                 | 4 78   | 57                          | 20 5                        | 13 2*                            |  | 18*   |
|  | 2-3   | 6 37                 | 5 99   | 50                          | 19 6                        | 15 2*                            |  | 20*   |
|  | 10-11 | 1 87                 | 1 76   | 222                         |                             | 14 9*                            |  | 21*   |
|  | 11-12 | 0 88                 | 0 83   | 361                         | 26 1                        | 11 5                             | 12 6   | 23  |
|  |       |                      |  |                             |                             |                                  |  |   |
|  |       |                      |  |                             |                             |                                  |  |   |

TABLE 3—Continued

|   | Time  | V<br>Urine<br>volume<br>cc per<br>minute | V cor<br>Urine volume<br>corrected for body<br>size by factor<br>1.73 from table 2<br>Area | U<br>Urine urea<br>nitrogen<br>mgm<br>per 100 cc | B<br>Blood urea<br>nitrogen<br>mgm<br>per 100 cc | $\frac{UV \text{ cor}}{B}$<br>Observed<br>clearance* | $\frac{U\sqrt{V} \text{ cor}}{B}$<br>Calculated stand<br>ard below<br>clearance (for V)<br>augmentation<br>limit | Per cent<br>of average<br>normal<br>clearance |
|---|-------|--|--|--|--|--|--|---|
| Exp 20-a Cic<br>9 a m, 100 cc of water Venous blood<br>Exp 20 b Cic<br>9 a m, 100 cc of water Venous blood<br>Exp 20 c Cic<br>9 a m, 100 cc of water Venous blood<br>Exp No 22 Cic<br>7 30 a m, breakfast with 15 grams urea<br>and 1000 cc of water 11 50 a m,<br>lunch with 1000 cc of water 1 20<br>and 2 05 p m, 500 cc of water each<br>time Cutaneous blood | 10-11 | 0 37                                     | 0 39   | 384  | 16 2   | 9 1  | 14 8   | 27  |
|   | 11-12 | 0 60                                     | 0 63   | 386  |  | 15 0   | 19 0   | 35  |
|   | 10-11 | 0 50                                     | 0 53   | 347  | 15 2   | 11 9   | 16 6   | 31  |
|   | 11-12 | 0 35                                     | 0 37   | 270  |  | 6 6  | 10 8   | 20  |
|   | 10-11 | 1 27                                     | 1 33   | 198  | 12 1   | 21 7   | 18 9   | 35  |
|   | 11-12 | 0 92                                     | 0 97   | 299  |  | 23 8   | 24 3   | 45  |
|   | 9-10  | 1 92                                     | 2 02   | 354  | 36 6   | 19 4*  |  | 26*   |
|   | 10-11 | 1 87                                     | 1 96   | 344  | 35 1   | 19 2*  |  | 26*   |
|   | 11-12 | 1 83                                     | 1 92   | 345  | 34 5   | 19 2*  |  | 26*   |
|   | 12-1  | 2 17                                     | 2 28   | 349  | 34 6   | 22 9*  |  | 31*   |
|   | 1-2   | 4 17                                     | 4 38   | 209  | 37 0   | 24 7*  |  | 33*   |
|   | 2-3   | 4 50                                     | 4 73   | 230  | 35 4   | 30 7*  |  | 41*   |
|   | 3-4   | 4 83                                     | 5 07   | 185  | 33 8   | 27 8*  |  | 37*   |
|   | 9-10  | 1 10                                     | 1 03   | 244  | 21 8   | 11 6   | 11 3   | 21  |
| Exp No 14 Val<br>8 a m, breakfast with 100 cc of water<br>12 noon lunch with 1000 cc of water<br>1 40 p m, 500 cc of water Cutane-<br>ous blood<br>Exp No 14-a Val<br>9 a m, 100 cc. of water Venous blood  | 10-11 | 0 97                                     | 0 91   | 265  | 19 4   | 12 4   | 13 1   | 24  |
|   | 11-12 | 0 90                                     | 0 85   | 285  | 18 9   | 12 9   | 13 9   | 25  |
|   | 12-1  | 2 17                                     | 2 04   | 135  | 22 1   | 12 5*  |  | 17*   |
|   | 1-2   | 5 08                                     | 4 78   | 57   | 20 5   | 13 2*  |  | 18*   |
|   | 2-3   | 6 37                                     | 5 99   | 50   | 19 6   | 15 2*  |  | 20*   |
|   | 10-11 | 1 87                                     | 1 76   | 222  |  | 14 9*  |  | 21*   |
|   | 11-12 | 0 88                                     | 0 83   | 361  | 26 1   | 11 5   | 12 6   | 23  |

TABLE 3—Continued

|   | Time                   | V<br>Urine<br>volume<br>cc per<br>minute | V cor<br>Urine volume<br>corrected for body<br>size by factor<br>$\frac{1.73}{\text{Area}}$ from table 2 | U<br>Urine urea<br>nitrogen<br>mgm<br>per 100 cc | B<br>Blood urea<br>nitrogen<br>mgm<br>per 100 cc | $\frac{UV \text{ cor}}{B}$<br>Observed<br>clearance* | $\frac{U\sqrt{V \text{ cor}}}{B}$<br>Calculated stand<br>ard below<br>clearance (for V)<br>augmentation<br>limit<br>cc blood per<br>minute | Per cent<br>of average<br>normal<br>clearance |
|---|------------------------|--|--|--|--|--|--|---|
| Exp A-24 Gm<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 1 02                                     | 0 97   | 269  | 34 8   | 7 4  | 7 61   | 14  |
| Exp A-25 Gm<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 80                                     | 0 76   | 314  | 35 3   | 6 8  | 7 76   | 14  |
| Exp A-26 Gm<br>9 05 a m, 100 cc of water<br>blood Venous  | 9-11                   | 1 04                                     | 0 99   | 339  | 37 0   | 9 0  | 9 10   | 17  |
| Exp A-27 Gm<br>8 25 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 97                                     | 0 92   | 388  | 44 6   | 8 1  | 8 36   | 15  |
| Exp A-28 Gm<br>8 30 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 97                                     | 0 92   | 362  | 39 4   | 8 4  | 8 82   | 16  |
| Exp A-29 Gm<br>6 a m, 30 grams urea and 500 cc of<br>water 7, 8, 9, 10, and 11 a m, 500 cc<br>of water each time Venous blood | 9-10<br>10-11<br>11-12 | 2 17<br>3 37<br>4 17                     | 2 06<br>3 20<br>3 96   | 362<br>268<br>209                                | 71 9<br>70 4<br>69 0                             | 10 3*<br>12 2*<br>12 1*                              |  | 14*<br>16*<br>16*                             |
| Exp A-30 Gm<br>8 25 a m, 100 cc. of water<br>blood Venous   | 9-11                   | 1 17                                     | 1 11   | 435  | 49 9   | 9 7  | 9 19   | 17  |

TABLE 3—Concluded

|   | Time                   | V<br>Urine<br>volume<br>cc per<br>minute | V cor<br>Urine volume<br>corrected for body<br>size by factor<br>$\frac{1.73}{\text{Area}}$ | U<br>Urine urea<br>nitrogen<br>mgm<br>per 100 cc | B<br>Blood urea<br>nitrogen<br>mgm<br>per 100 cc | $\frac{UV \text{ cor}}{B}$<br>Observed<br>clearance* | $\frac{U \sqrt{V} \text{ cor}}{B}$<br>Calculated stand<br>ard below<br>clearance (for V)<br>augmentation<br>limit<br>cc blood per<br>minute | Per cent<br>of average<br>normal<br>clearance |
|---|------------------------|--|---|--|--|--|---|---|
| Exp A-24 Gm<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 1 02                                     | 0 97  | 269  | 34 8   | 7 4  | 7 61  | 14  |
| Exp A-25 Gm<br>8 20 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 80                                     | 0 76  | 314  | 35 3   | 6 8  | 7 76  | 14  |
| Exp A-26 Gm<br>9 05 a m, 100 cc of water<br>blood Venous  | 9-11                   | 1 04                                     | 0 99  | 339  | 37 0   | 9 0  | 9 10  | 17  |
| Exp A-27 Gm<br>8 25 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 97                                     | 0 92  | 388  | 44 6   | 8 1  | 8 36  | 15  |
| Exp A-28 Gm<br>8 30 a m, 100 cc of water<br>blood Venous  | 9-11                   | 0 97                                     | 0 92  | 362  | 39 4   | 8 4  | 8 82  | 16  |
| Exp A-29 Gm<br>6 a m, 30 grams urea and 500 cc of<br>water 7, 8, 9, 10, and 11 a m, 500 cc<br>of water each time Venous blood | 9-10<br>10-11<br>11-12 | 2 17<br>3 37<br>4 17                     | 2 06<br>3 20<br>3 96  | 362<br>268<br>209                                | 71 9<br>70 4<br>69 0                             | 10 3*<br>12 2*<br>12 1*                              |   | 14*<br>16*<br>16*                             |
| Exp A-30 Gm<br>8 25 a m, 100 cc. of water<br>blood Venous   | 9-11                   | 1 17                                     | 1 11  | 435  | 49 9   | 9 7  | 9 19  | 17  |







In figure 7 the same urea excretion curve as the one given in figure 5 has been plotted on logarithmic paper. In the logarithmic curve variations in height are proportional to *percentage* changes, rather than absolute changes, in the data plotted. In a uremic case, the clearance values are all so low that variations on them are inconspicuous, when plotted on an ordinary scale, as in figure 5. But when plotted logarithmically, as in figure 7, they are as evident as the clearance variations of a normal subject.

The values for the augmentation limits, given in table 4, are on the whole somewhat lower than those found for normal subjects in the preceding paper (6). The average figures for nephritic and normal subjects are 1.73 and 2.13 cc per minute respectively. The decrease in augmentation limit is hardly great enough to justify the conclusion that it represents an effect of the disease. It is not very significant compared with the relatively great fall in the *level* of the curves observed in cases with damaged renal function.

In each case there is, compared with the normal, a fall of nearly equal proportions in the *level* of the ascending line and in that of the horizontal line reached at the augmentation limits, with relatively small change in the limit. Consequently the standard blood urea clearance, indicated by the height of the ascending line at  $V = 1$  cc per minute, and the maximum clearance, indicated by the height at the augmentation limit and beyond, show in these cases approximately equal percentage diminutions below the normal. The similarity in the significance of results by the maximum and standard clearance determinations is also indicated by the agreement between the percentages of normal values shown by the two clearances for each individual, indicated by the figures with and without stars respectively in the last column of table 3.

In table 4 the variations for the standard and maximum clearances in each patient are given. The table shows that, as previously found with normal individuals, the average variation in a given subject is slightly greater for the standard clearance than for the maximum clearance.

In figure 8 all the curves are presented, with scales indicating the per cent of normal standard and maximum clearance observed in each case. It is apparent that both clearances tend to show about the same percentage fall in cases with renal deficiency.

In figure 7 the same urea excretion curve as the one given in figure 5 has been plotted on logarithmic paper. In the logarithmic curve variations in height are proportional to *percentage* changes, rather than absolute changes, in the data plotted. In a uremic case, the clearance values are all so low that variations on them are inconspicuous, when plotted on an ordinary scale, as in figure 5. But when plotted logarithmically, as in figure 7, they are as evident as the clearance variations of a normal subject.

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In figure 8 all the curves are presented, with scales indicating the per cent of normal standard and maximum clearance observed in each case. It is apparent that both clearances tend to show about the same percentage fall in cases with renal deficiency.

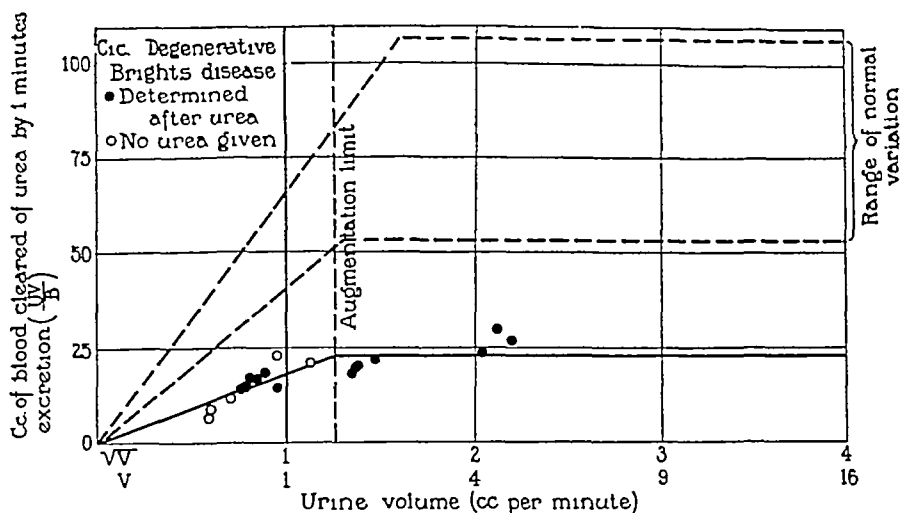


FIG 3 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT C.C.

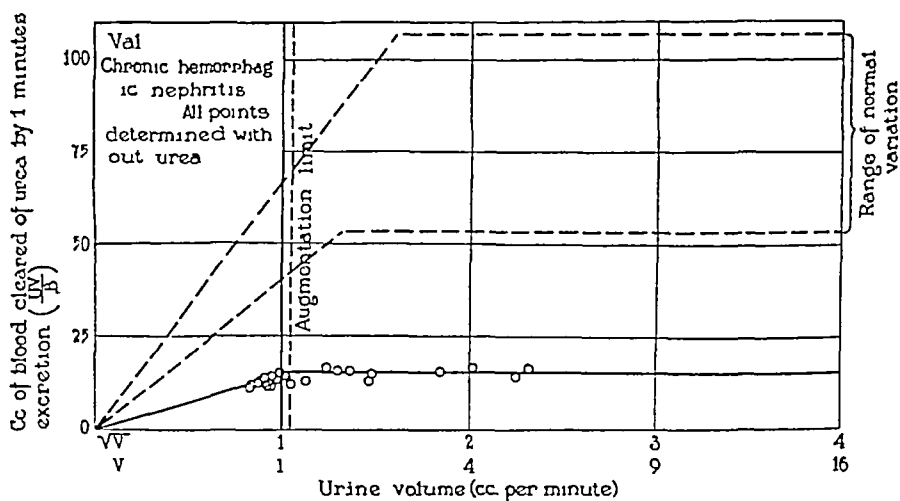


FIG 4 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT VAL

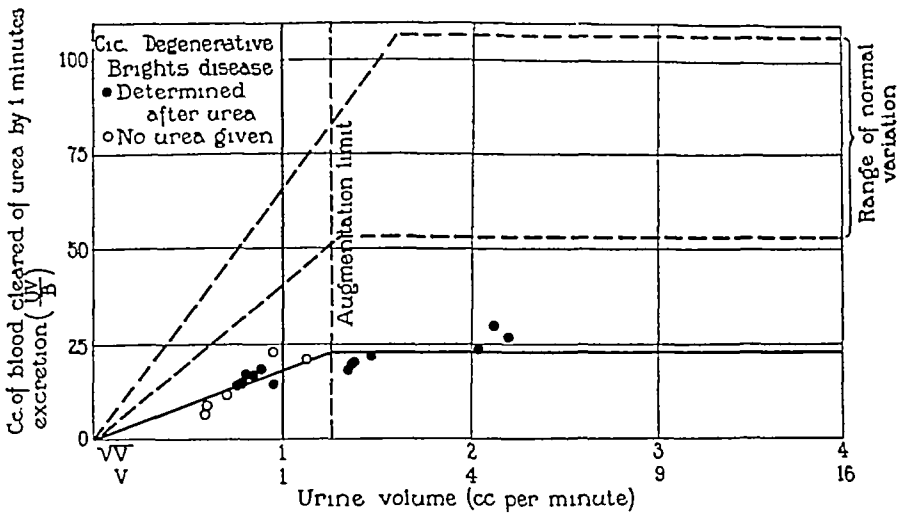


FIG 3 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT CIC.

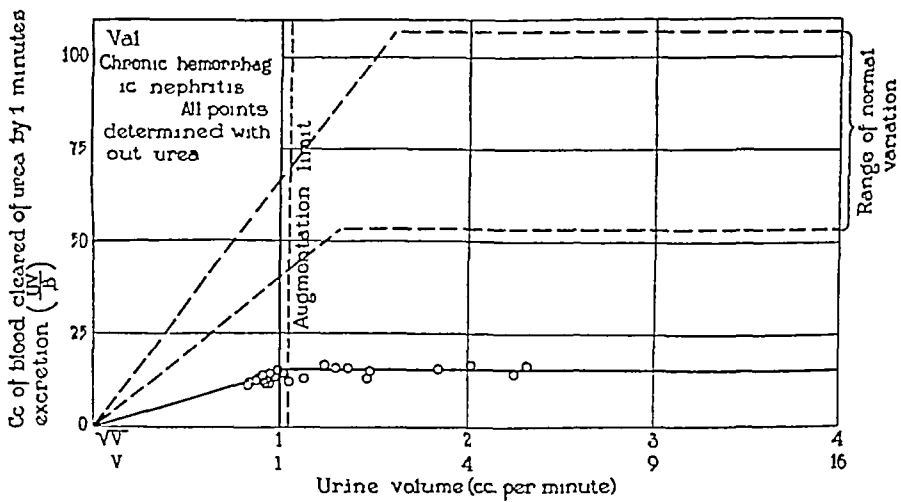


FIG 4 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT VAL

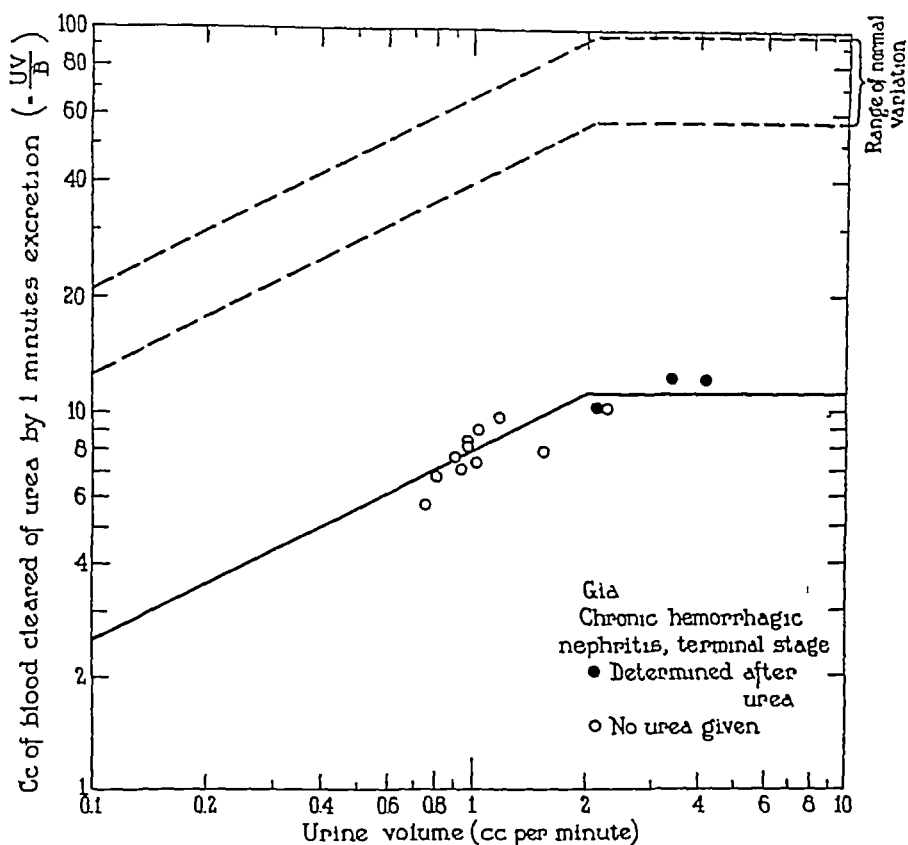


FIG 7 THE SAME UREA CLEARANCE CURVE AS THE ONE GIVEN IN FIGURE 5 BUT HERE PLOTTED ON LOGARITHMIC PAPER

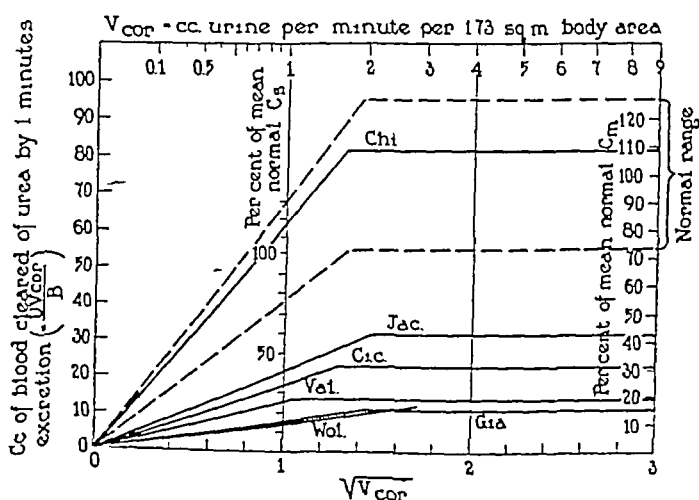


FIG 8 CURVES OF THE SIX PATIENTS, SHOWING RELATIVE EFFECTS OF RENAL DEFICIENCY OF EACH ON STANDARD AND MAXIMUM CLEARANCES

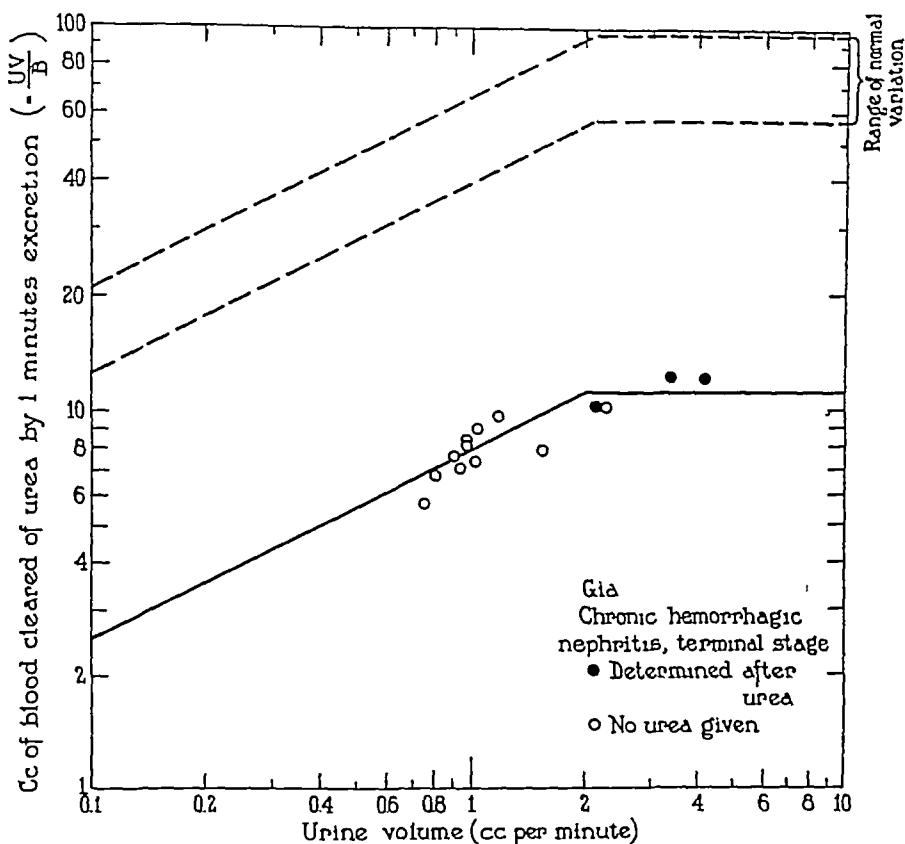


FIG 7 THE SAME UREA CLEARANCE CURVE AS THE ONE GIVEN IN FIGURE 5 BUT HERE PLOTTED ON LOGARITHMIC PAPER

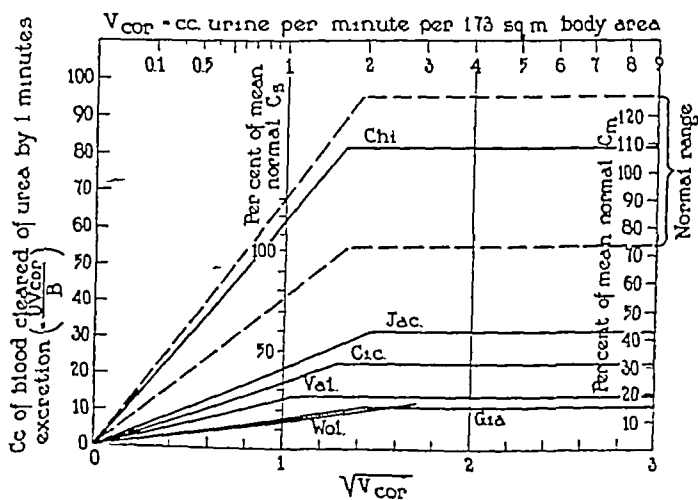


FIG 8 CURVES OF THE SIX PATIENTS, SHOWING RELATIVE EFFECTS OF RENAL DEFICIENCY OF EACH ON STANDARD AND MAXIMUM CLEARANCES

urine volumes above the augmentation limit of about 2 cc per minute, proved to be equally sensitive as indicators of renal function in these nephritics

4 Our data confirm MacKay and MacKay (3) in showing that loss of renal function may exceed 60 per cent before the blood urea content rises above the highest level observed in normal subjects Unless the excretion rate is also considered, the blood urea, taken alone, may fail to reveal diminishing renal ability until the latter has reached an advanced stage

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## METHODS

In each experiment observations were made over a 24-hour period, from 6 a m one morning until 6 a m on the next day. Hourly urine specimens were collected from 6 a.m. until 10 p m, and then a single specimen was collected between 10 p m and 6 a m. When the subject was unable to void or there was doubt concerning the completeness of voiding the hour period was extended to 2 hours. A sample of blood was drawn by vein puncture at 6 30 a m, the middle of the first urine collection period, and then at the middle of each second hour thereafter until 8 30 p m. The blood urea values for the intermediate hours were obtained by interpolation. A sample was drawn at 9 30 p m for the last urine period of the day, and another at 6 a m on the following morning. The average value of these two samples served as the blood urea concentration from which the standard clearance of the night period was calculated. Urine collections were made within 2 minutes, and the blood samples were drawn within 5 minutes of the stated time. The blood and urine urea concentrations were determined gasometrically (7). The standard clearance,

$C_s = \frac{U}{B} \sqrt{V_c}$ , where  $U$  is the urine urea concentration,  $B$  the blood

urea concentration, and  $V$  the urine volume in cubic centimeters per minute, was calculated as previously described (4, 5). The urine volume, is corrected in each case to  $V_c$  by the use of a factor dependent on the ideal body surface of the subject. On the charts the standard clearance has been recorded as the actual value and as a per cent of the normal mean of 54 cc per minute. When  $V_c$  was above the augmentation limit of 2 the rate of urea excretion has been calculated on the

basis of the maximum blood urea clearance,  $\frac{U \sqrt{V_c}}{B}$  (5). These

are recorded in the figures as a per cent of the mean normal, 75 cc per minute, but have not been used in determining the variability of the rate of urea excretion.

The normal subjects on whom observations were made were up and about during the course of the experiments. All of the patients suffering from Bright's disease were confined to bed. None of the latter received any coffee with their meals, while the normal subjects

## METHODS

In each experiment observations were made over a 24-hour period, from 6 a m one morning until 6 a m on the next day. Hourly urine specimens were collected from 6 a.m. until 10 p m, and then a single specimen was collected between 10 p m and 6 a m. When the subject was unable to void or there was doubt concerning the completeness of voiding the hour period was extended to 2 hours. A sample of blood was drawn by vein puncture at 6 30 a m, the middle of the first urine collection period, and then at the middle of each second hour thereafter until 8 30 p m. The blood urea values for the intermediate hours were obtained by interpolation. A sample was drawn at 9 30 p m for the last urine period of the day, and another at 6 a m on the following morning. The average value of these two samples served as the blood urea concentration from which the standard clearance of the night period was calculated. Urine collections were made within 2 minutes, and the blood samples were drawn within 5 minutes of the stated time. The blood and urine urea concentrations were determined gasometrically (7). The standard clearance,

$C_s = \frac{U}{B} \sqrt{V_c}$ , where  $U$  is the urine urea concentration,  $B$  the blood

urea concentration, and  $V$  the urine volume in cubic centimeters per minute, was calculated as previously described (4, 5). The urine volume, is corrected in each case to  $V_c$  by the use of a factor dependent on the ideal body surface of the subject. On the charts the standard clearance has been recorded as the actual value and as a per cent of the normal mean of 54 cc per minute. When  $V_c$  was above the augmentation limit of 2 the rate of urea excretion has been calculated on the

basis of the maximum blood urea clearance,  $\frac{U \sqrt{V_c}}{B}$  (5). These

are recorded in the figures as a per cent of the mean normal, 75 cc per minute, but have not been used in determining the variability of the rate of urea excretion.

The normal subjects on whom observations were made were up and about during the course of the experiments. All of the patients suffering from Bright's disease were confined to bed. None of the latter received any coffee with their meals, while the normal subjects

Observations on 5 patients with degenerative Bright's disease are given in figure 3 With the exception of case no 12, one on whom

Fig. 3  
Clinical and laboratory observations

| Case number | Hospital number | Diagnosis            |                  | Complications         | Age                               | Sex | Heart size         | Blood pressure | Eye grounds                | Edema  | Urea excretion (mg/100 ml) |      |
|-------------|-----------------|----------------------|------------------|-----------------------|-----------------------------------|-----|--------------------|----------------|----------------------------|--------|----------------------------|------|
|             |                 | Bright's disease     |                  |                       |                                   |     |                    |                |                            |        |                            |      |
|             |                 | Type                 | Stage            |                       |                                   |     |                    |                |                            |        |                            |      |
| 5           | 6458            | Hemorrhagic          | Initial—latent   | Acute sinusitis       | 49                                | M   | Normal             | 155/106        | Normal                     | 0      | 35.0                       |      |
| 6           | 6164            | Hemorrhagic          | Healed           |                       | 31                                | M   | Normal             | 125/65         | Normal                     | 0      | 20.0                       |      |
| 7           | 6475            | Hemorrhagic          | Active           |                       | 25                                | F   | Normal             | 168/114        | Normal                     | ++     | 27.0                       |      |
| 8           | 6139            | Hemorrhagic          | Latent           |                       | 19                                | M   | Normal             | 152/ 94        | Normal                     | 0      | 43.0                       |      |
| 9           | 6162            | Hemorrhagic          | Latent           |                       | 20                                | F   | Slightly increased | 202/115        | Normal                     | 0      | 28.0                       |      |
| 10          | 6238            | Hemorrhagic          | Initial—terminal | Cardiac insufficiency | 16                                | M   | Increased          | 136/ 86        | Normal                     | 0      | 44.0                       |      |
| 11          | 6166            | Hemorrhagic          | Terminal         |                       | 34                                | F   | Increased          | 203/118        | Retinitis with hemorrhages | +      | 25.0                       |      |
| 12          | 6184            | Degenerative cryptic | Active           |                       | 18                                | M   | Normal             | 106/ 77        | Normal                     | +++    | 23.0                       |      |
| 13          | 6473            | Degenerative cryptic | Initial          |                       | 12                                | M   | Normal             | 115/ 70        | Normal                     | +++    | 28.0                       |      |
| 14          | 6172            | Degenerative cryptic | Active           |                       | Pulmonary tuberculosis<br>Empyema | 29  | M                  | Normal         | 110/ 68                    | Normal | —                          | 30.0 |
| 15          | 5949            | Degenerative cryptic | Terminal         | 20                    |                                   | M   | Normal             | 128/ 83        | Normal                     | +++    | 57.0                       |      |
| 16          | 5505            | Degenerative cryptic | Terminal         | 11                    |                                   | M   | Normal             | 116/ 60        | Normal                     | ++     | 42.0                       |      |
| 17          | 6446            | Arteriosclerotic     |                  | 49                    |                                   | F   | Normal             | 234/154        | Normal                     | 0      | 16.0                       |      |
| 18          | 6102            | Arteriosclerotic     |                  | 51                    |                                   | F   | Slightly increased | 148/ 86        | Normal                     | 0      | 3.6                        |      |
| 19          | 6466            | Arteriosclerotic     |                  | Cardiac failure       | 49                                | F   | Greatly increased  | 242/145        | Retinitis                  | +      | 57.0                       |      |
| 20          | 5210            | Hemorrhagic          |                  | Terminal              | Otitis media                      | 30  | M                  | Normal         | 148/190                    | Normal | 0                          | 41.0 |
| 21          | 5482            | Hemorrhagic          |                  | Active                |                                   | 12  | M                  | Normal         | 152/110                    | Normal | +                          | 22.0 |

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Observations on 5 patients with degenerative Bright's disease are given in figure 3 With the exception of case no 12, one on whom

| Case number | Hospital number | Diagnosis            |                  | Complications                     | Age | Sex                | Heart size         | Blood pressure |    |
|-------------|-----------------|----------------------|------------------|-----------------------------------|-----|--------------------|--------------------|----------------|----|
|             |                 | Bright's disease     |                  |                                   |     |                    |                    |                |    |
|             |                 | Type                 | Stage            |                                   |     |                    |                    |                |    |
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| 12          | 6184            | Degenerative cryptic | Active           |                                   | 18  | M                  | Normal             | 106/ 77        | No |
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| 20          | 5210            | Hemorrhagic          | Terminal         | Otitis media                      | 30  | M                  | Normal             | 148/190        | No |
| 21          | 5482            | Hemorrhagic          | Active           |                                   | 12  | M                  | Normal             | 152/110        | No |

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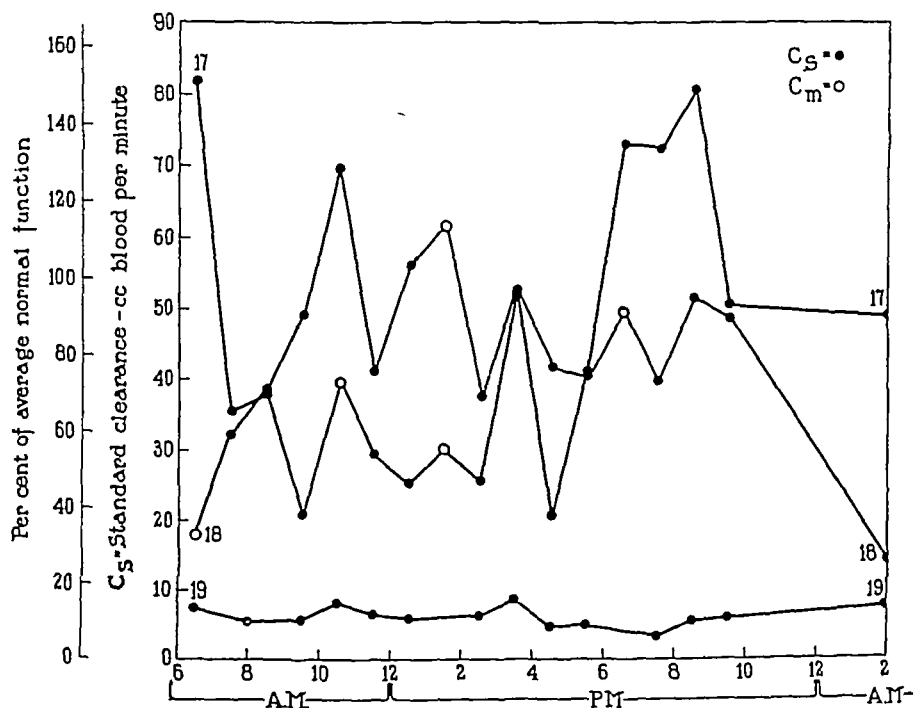


FIG 4 ARTERIOSCLEROTIC BRIGHT'S DISEASE

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In order to ascertain whether it is necessary to carry out this urea excretion test in the fasting state a series of observations were made on two patients with hemorrhagic Bright's disease Observations were made for two hours, from 6 to 8 a m before breakfast, and for two other hour periods, 9 to 11 a m after breakfast The tests were

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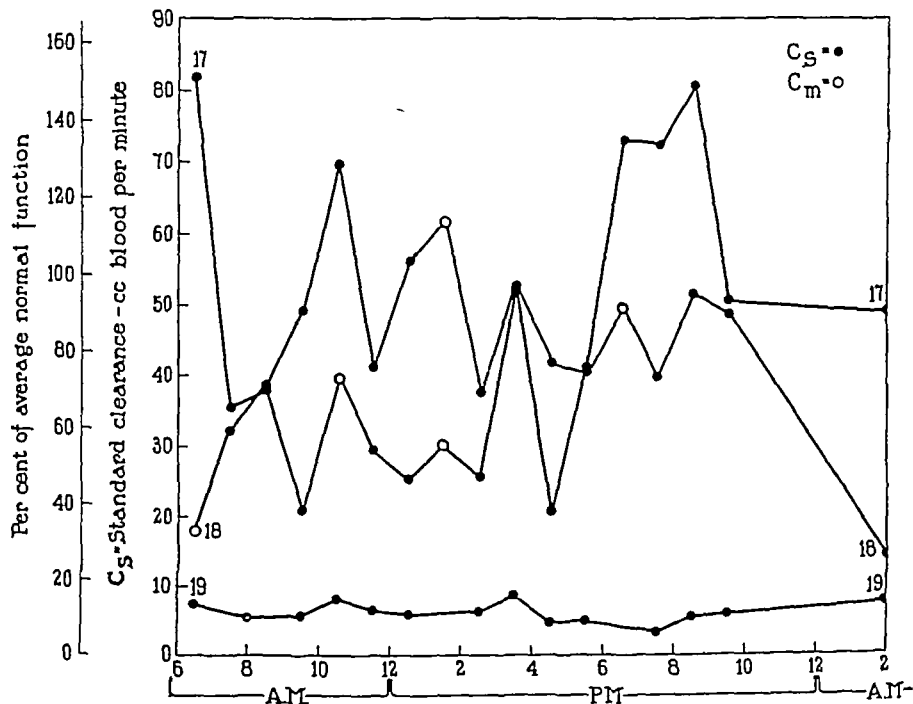


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The experiments detailed in table 3 indicate that there is less variability in a series of observations made on an individual on different days, but at the same time each day, than in a series of observations all made on the same day.

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The method, in brief, consists of the determination of total base,  $\text{CO}_2$ , Cl, inorganic phosphate and protein of serum. The serum was obtained from arterial blood or venous blood (without stasis) which had been secured and treated, by techniques already described, in such a manner as to prevent all air contact.

The procedures for determining  $\text{CO}_2$  and Cl have not been changed and the values for these factors previously given need no revision. For total base a modification of Stadie's (3) adaptation of Fiske's method has been employed in the recent studies. We have isolated and analyzed the benzidine sulfate instead of titrating the benzidine filtrate as Stadie recommended. Previously reported base determinations were made by a technique in which phosphates were not removed, but were, supposedly converted to a form in which they combined

TABLE 1  
*Total base concentration in normal serum*

| Subject | Sex    | Age | Total base   |
|---------|--------|-----|--------------|
|         |        |     | <i>m -eq</i> |
| D M     | Male   | 29  | 154.4        |
|         |        |     | 157.2        |
|         |        |     | 155.7        |
|         |        |     | 156.3        |
| H O     | Male   | 27  | 153.0        |
| F B     | Male   | 30  | 153.6        |
| L D     | Male   | 27  | 152.5        |
| M W     | Male   | 30  | 155.0        |
| E D     | Male   | 26  | 153.0        |
| J P     | Male   | 40  | 154.0        |
| A J     | Female | 28  | 153.0        |
| R I     | Female | 31  | 152.5        |
| H D     | Female | 15  | 158.0        |
| A A     | Female | 16  | 152.0        |

with a definite equivalent of base. Subsequent investigation showed that it was impossible to insure conversion of phosphates to such a stable form with any regularity.

Earlier base determinations were subject to an error, the magnitude of which depended upon the amount of inorganic phosphate in the serum, varying from +1 to -1 equivalent of base for every equivalent of P in serum. As the serum of normal resting adults contains only from 1 to 3 milliequivalents of inorganic P, the error is of little significance. It may, however, attain a considerable magnitude in subjects with advanced chronic nephritis with high serum phosphates.

Fifteen analyses of the sera of 11 normal young adults (medical students, physicians and laboratory workers) carried out by the new technique in this laboratory by Oard and Lee reveal a greater constancy in the concentration of total base than did the determinations reported earlier. See table 1.

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ratio is abnormal, calculations based on determinations of total protein only and assumption of an average ratio may be subject to significant errors. Such errors are of little importance in dealing with normal blood as can be seen in table 2. They might attain a considerable importance in pathologic conditions associated with abnormal serum albumin globulin ratios. Fortunately in these conditions the total protein concentration is usually low and the error correspondingly diminished.

The present work has included determination of serum pH only in rare instances. For the purposes of calculating base combined with protein an average pH value of 7.35 has been assumed. The equations given above are, therefore, simplified to

$$BP_{(alb)} = 2.733 P$$

$$BP_{(glob)} = 1.869 P$$

$$BP_{(prot.)} = 2.476 P (A/G = 1.8)$$

Such simplification, although obviously necessary if the total procedure is to be made generally applicable to the study of clinical problems, introduces into the calculations another error.

Phosphate combining equivalents are also calculated with the assumption of a constant pH of 7.35. At this pH 80 per cent of the phosphate exists in the dibasic form  $HPO_4$  and the ratio  $\frac{HPO_4}{H_2PO_4}$  vary in the same direction, as the reaction of the blood changes.

The total errors entailed in the assumption of a constant pH are seldom of important magnitude. If inorganic P were as high as 19 mgm per 100 cc and pH as low as 7.00, phosphate equivalents calculated by the formula that has been employed would give a value only 1 m. eq. too high. If in the same serum the total protein concentration were 7.00 per cent, the value obtained for BP would be 2.5 m. eq. too great. If the A/G ratio were only 1.0, a further positive error of 1.5 m. eq. would be introduced. The total error in this extreme case in the estimation of base combined with protein and phosphate would be +5.0 m. eq. with a negative error of the same magnitude in the undetermined acid value. In the actual analyses presented errors never attained such magnitude because high phosphorus and low pH were usually associated with reduced proteins.

The new "total base" method was introduced in November, 1925. In the tables, then, base values of earlier dates may be in error by as much as the equivalents of inorganic P found in the serum. If proteins were fractionated it is indicated in the tables. When non-protein nitrogen of serum has been determined it is indicated in the tables by the letter *s* after the non-protein nitrogen value. In all other instances whole blood non-protein nitrogen has been used for correction of the serum protein values.

If the newer factors and methods are employed for the estimation of the acid-base equilibrium of serum the concentration of the base combined with "undetermined acids" (sulfate + organic acids) seldom exceeds and is usually considerably less than 10 milliequivalents.

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TABLE 3

Data in nephritic patients

| Number | Date        | Weight<br>kgm | Edema | Vomiting | O <sub>2</sub> capacity<br>vol<br>unics<br>per<br>cent | Cell volume | Serum total protein | HCO <sub>3</sub> | Cl    | Inorganic P | Acid 1+2+3+4 | Base  | Undetermined acid<br>6-5 | Non protein nitro-<br>gen<br>mgm<br>per<br>100<br>cc | Phthalein per cent<br>in 2 hrs. | Treatment and remarks  |
|--------|-------------|---------------|-------|----------|--|-------------|---------------------|------------------|-------|-------------|--------------|-------|--------------------------|--|---------------------------------|--|
| 29767  | 1924        |               |       |          |  |             |                     |                  |       |             |              |       |                          |  |                                 |  |
|        | February 19 | 67.8          | 0     | 0        | 14.8   | 29.4        | 16.5                | 19.0             | 102.7 | 3.1         | 141.3        |       |                          | 85   | 18                              | After salt poor diet   |
|        | February 25 | 66.4          | 0     | 0        | 15.0   | 32.6        | 17.5                | 18.1             | 100.0 | 2.9         | 138.5        |       |                          | 75   |                                 | After 2 days of low fluid + 5 grams NaCl                         |
|        | February 29 | 66.0          | 0     | 0        | 14.3   | 32.5        | 16.7                | 18.8             | 105.3 | 3.2         | 144.0        |       |                          | 69   |                                 | After 8 days of high fluid + 5 grams NaCl                        |
|        | March 8     | 68.2          | 0     | 0        | 13.8   | 31.3        | 15.5                | 19.5             | 104.4 | 2.2         | 131.6        |       |                          | 44   |                                 |  |
|        | 1925        |               |       |          |  |             |                     |                  |       |             |              |       |                          |  |                                 |  |
|        | January 14  |               | 0     | 0        | 12.7   |             | 17.1                | 16.3             | 109.0 | 6.5         | 148.9        | 183.7 | 34.8                     | 75   |                                 | Ambulatory Without symptoms                                      |
|        | November 19 | 59.0          | 0     | +        | 8.7  | 23.0        | 16.4                | 9.8              | 105.5 | 5.5         | 137.2        | 173.0 | 35.8                     | 167  |                                 | Uremia   |
|        | November 27 | 59.0          | 0     | +        | 8.4  | 21.3        | 15.6                | 8.2              | 96.4  | 5.4         | 125.6        | 132.9 | 7.3                      | 168  |                                 |  |
|        | December 1  |               | 0     | +        | 7.3  | 17.1        | 12.6                | 13.3             | 95.3  | 5.4         | 126.6        | 148.0 | 21.4                     | 167  |                                 | Coma Bicarbonate and saline on November 30                       |
| 60345  | December 6  |               | 0     | +        | 5.9  | 17.1        | 15.3                | 14.2             | 96.2  | 7.4         | 133.1        | 137.5 | 4.4                      | 163  |                                 | Convulsions. Before and after intravenous MgSO <sub>4</sub>      |
|        | December 11 |               | 0     | +        | 6.3  | 16.3        | 15.3                | 12.6             | 94.3  | 7.4         | 129.6        | 140.6 | 11.0                     | 158  |                                 | Before and after intravenous MgSO <sub>4</sub>                   |
|        | December 17 |               | 0     | 0        | 5.4  | 15.4        | 13.9                | 10.5             | 102.4 | 4.8         | 132.2        | 133.6 | 1.4                      | 145  |                                 | Rational Free from symptoms. After frequent subcutaneous saline  |
|        | 1926        |               |       |          |  |             |                     |                  |       |             |              |       |                          |  |                                 |  |
|        | January 2   | 51.8          | 0     | +        | 7.1  | 18.3        | 16.1                | 6.8              | 94.4  | 5.7         | 123.0        | 128.1 | 5.1                      | 165  |                                 | Ascending urinary infection After 10 days of negative Cl balance |
|        | January 9   |               | +     | +        | 5.1  | 14.9        | 11.1                | 4.5              | 90.8  | 5.6         | 112.0        | 120.5 | 8.5                      | 171  |                                 | Heart failure Comatose Has received subcutaneous NaCl            |
|        | 1927        |               |       |          |  |             |                     |                  |       |             |              |       |                          |  |                                 | Died January 11  |
|        | April 20    | 52.7          | +     | +        | 7.2  | 20.5        | 14.6                | 17.3             | 102.4 | 3.5         | 137.8        | 148.2 | 10.4                     | 117  |                                 | Heart failure  |
|        | April 25    | 49.1          | 0     | +        | 8.0  | 17.1        | 15.5                | 16.5             | 103.2 | 5.0         | 140.2        | 148.0 | 7.8                      | 122  |                                 | After diuresis and negative Cl balance                           |
|        | May 3       | 49.8          | 0     | +        | 6.7  | 17.6        | 15.8                | 16.3             | 105.6 | 4.2         | 141.9        | 145.9 | 4.0                      | 118  |                                 | Positive Cl balance  |
| 56247  | May 10      | 51.6          | 0     | 0        | 6.8  | 17.3        | 13.4                | 16.8             | 106.6 | 4.2         | 141.0        | 149.1 | 8.1                      | 112  |                                 | Positive Cl balance  |
|        | May 17      | 51.6          | 0     | 0        | 5.0  | 16.1        | 14.9                | 16.3             | 110.0 | 4.9         | 146.1        | 154.5 | 8.4                      | 124  |                                 | Cl equilibrium   |
|        | May 27      | 51.2          | 0     | +        | 5.7  | 17.5        | 15.4                | 17.8             | 103.8 | 4.7         | 141.7        | 150.5 | 8.8                      | 123  |                                 | Negative Cl balance  |
|        | June 7      | 51.2          | 0     | 0        | 6.6  | 19.8        | 15.7                | 17.1             | 107.6 | 4.7         | 145.1        | 153.4 | 8.3                      | 94   |                                 | Positive Cl balance  |
|        | June 17     | 53.5          | 0     | 0        | 6.8  | 19.9        | 12.7                | 15.8             | 107.0 | 4.7         | 140.2        | 148.8 | 8.6                      | 98   |                                 | Positive Cl balance  |
|        | 1928        |               |       |          |  |             |                     |                  |       |             |              |       |                          |  |                                 | Died some months later   |
|        | December 27 | 65.7          | +     | +        | 10.7   | 41.8        | 12.5                | 25.0             | 106.8 | 3.5         | 147.8        | 154.3 | 6.5                      | 85   |                                 | Heart failure  |

TABLE 3  
Data in nephritic patients

| Number | Date        | Weight<br>kgm | Edema | Vomiting | O <sub>2</sub> capacity<br>l./min.<br>per cent | Cell volume<br>per cent | Serum total protein<br>gm | HCO <sub>3</sub> | Cl    | Inorganic P | Base  | Undetermined acid<br>6-5 | Non protein nitro-<br>gen | Phthalein per cent<br>in 2 hrs. | Treatment and remarks  |
|--------|-------------|---------------|-------|----------|--|-------------------------|---------------------------|------------------|-------|-------------|-------|--------------------------|---------------------------|---------------------------------|--|
|        |             |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 |  |
| 29267  | 1924        |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 |  |
|        | February 19 | 67.8          | 0     | 0        | 14.8   | 29.4                    | 16.5                      | 19.0             | 102.7 | 3.1         | 141.3 |                          | 85                        | 18                              | After salt poor diet   |
|        | February 25 | 66.4          | 0     | 0        | 15.0   | 32.6                    | 17.5                      | 18.1             | 100.0 | 2.9         | 138.5 |                          | 75                        |                                 | After 2 days of low fluid + 5 grams NaCl                         |
|        | February 29 | 66.0          | 0     | 0        | 14.3   | 32.5                    | 16.7                      | 18.8             | 105.3 | 3.2         | 144.0 |                          | 69                        |                                 | After 8 days of high fluid + 5 grams NaCl                        |
|        | March 8     | 68.2          | 0     | 0        | 13.8   | 31.3                    | 15.5                      | 19.5             | 104.4 | 2.2         | 131.6 |                          | 44                        |                                 |  |
|        | 1925        |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 |  |
|        | January 14  |               | 0     | 0        | 12.7   |                         | 17.1                      | 16.3             | 109.0 | 6.5         | 148.9 | 183.7                    | 34.8                      |                                 | Ambulatory Without symptoms                                      |
|        | November 19 | 59.0          | 0     | +        | 8.7  | 23.0                    | 16.4                      | 9.8              | 105.5 | 5.5         | 137.2 | 173.0                    | 35.8                      |                                 | Uremia   |
|        | November 27 | 59.0          | 0     | +        | 8.4  | 21.3                    | 15.6                      | 8.2              | 96.4  | 5.4         | 125.6 | 132.9                    | 7.3                       |                                 | Coma Bicarbonate and saline on November 30                       |
|        | December 1  |               | 0     | +        | 7.3  | 17.1                    | 12.6                      | 13.3             | 95.3  | 5.4         | 126.6 | 148.0                    | 21.4                      |                                 | Convulsions. Before and after intravenous MgSO <sub>4</sub>      |
| 60345  | December 6  |               | 0     | +        | 5.9  | 17.1                    | 15.3                      | 14.2             | 96.2  | 7.4         | 133.1 | 137.5                    | 4.4                       |                                 | Before and after intravenous MgSO <sub>4</sub>                   |
|        | December 11 |               | 0     | +        | 6.3  | 16.3                    | 15.3                      | 12.6             | 94.3  | 7.4         | 129.6 | 140.6                    | 11.0                      |                                 |  |
|        | December 17 |               | 0     | 0        | 4.9  | 15.3                    | 13.9                      | 10.5             | 102.4 | 4.8         | 132.2 | 133.6                    | 1.4                       |                                 | Rational Free from symptoms. After frequent subcutaneous saline  |
|        | 1926        |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 |  |
|        | January 2   | 51.8          | 0     | +        | 7.1  | 18.3                    | 16.1                      | 6.8              | 94.4  | 5.7         | 123.0 | 128.1                    | 5.1                       |                                 | Ascending urinary infection After 10 days of negative Cl balance |
|        | January 9   |               | +     | +        | 5.1  | 14.9                    | 11.1                      | 4.5              | 90.8  | 5.6         | 112.0 | 120.5                    | 8.5                       |                                 | Heart failure Comatose Has received subcutaneous NaCl            |
|        | 1927        |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 |  |
|        | April 20    | 52.7          | +     | +        | 7.2  | 20.5                    | 14.6                      | 17.3             | 102.4 | 3.5         | 137.8 | 148.2                    | 10.4                      |                                 | Heart failure  |
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|        | May 3       | 49.8          | 0     | +        | 6.7  | 17.6                    | 15.8                      | 16.3             | 105.6 | 4.2         | 141.9 | 145.9                    | 4.0                       |                                 | Positive Cl balance  |
| 56347  | May 10      | 51.6          | 0     | 0        | 6.8  | 17.3                    | 13.4                      | 16.8             | 106.6 | 4.2         | 141.0 | 149.1                    | 8.1                       |                                 | Positive Cl balance  |
|        | May 17      | 51.4          | 0     | 0        | 5.0  | 16.1                    | 14.9                      | 16.3             | 110.0 | 4.9         | 146.1 | 154.5                    | 8.4                       |                                 | Cl equilibrium   |
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|        | June 7      | 51.2          | 0     | 0        | 6.6  | 19.8                    | 15.7                      | 17.1             | 107.6 | 4.7         | 145.1 | 153.4                    | 8.3                       |                                 | Positive Cl balance  |
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|        | 1926        |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 |  |
|        | December 27 | 65.7          | +     | +        | 10.7   | 41.8                    | 12.5                      | 25.0             | 106.8 | 3.5         | 147.8 | 154.3                    | 6.5                       |                                 | Died some months later   |
|        |             |               |       |          |  |                         |                           |                  |       |             |       |                          |                           |                                 | Heart failure  |

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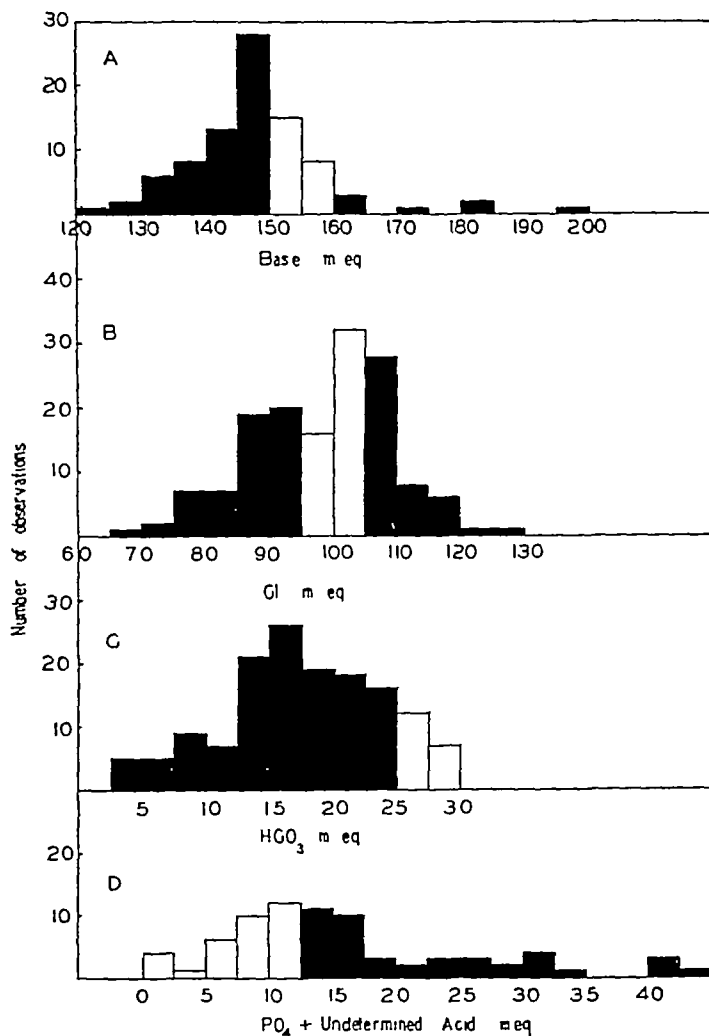


FIG 1 DISTRIBUTION OF VALUES FOR BASE, Cl, HCO<sub>3</sub> AND PO<sub>4</sub> + UNDETERMINED ACID

White columns indicate normal values, black columns abnormal values

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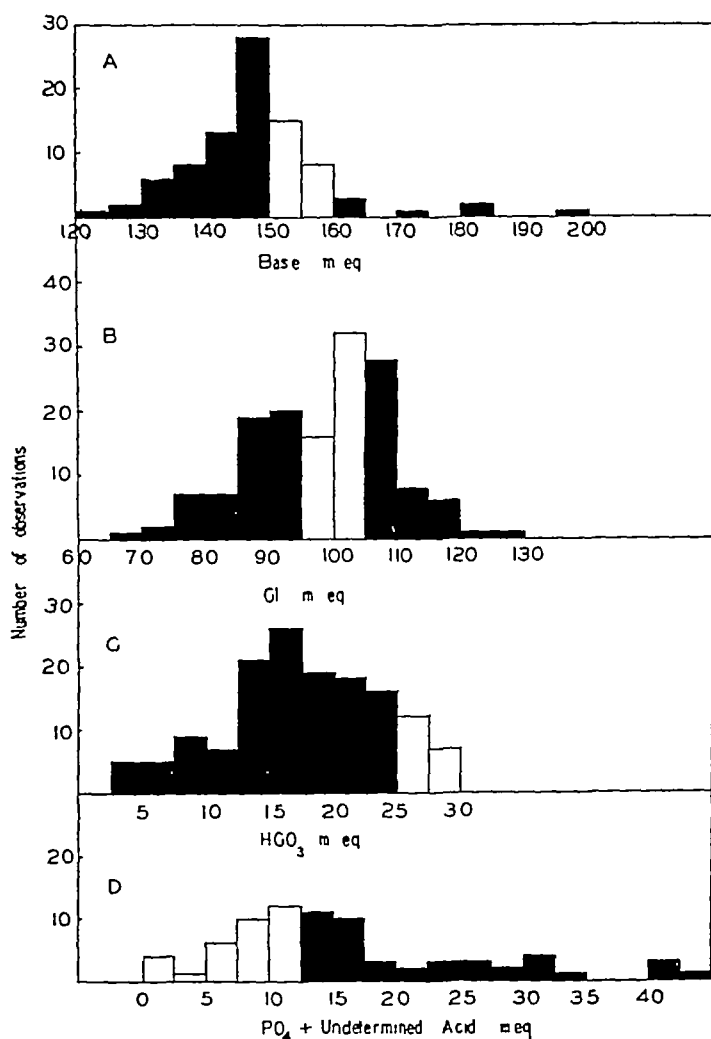


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persistent vomiting from other causes (6, 18) result in loss of Cl and compensatory increase of bicarbonate in serum. From the fact that vomiting of nephritis does not cause alkalosis one would be inclined to infer that the vomitus is relatively deficient in free acid.

*Phosphate, sulfate and organic acid as causes of acidosis*

Figure 1 D shows the frequency with which excessive quantities of  $\text{PO}_4$  + undetermined acids are encountered. That  $\text{PO}_4$  accumulation alone offers an inadequate explanation of nephritic acidosis has already been mentioned. Denis and associates (8) and others (9) have shown that the inorganic sulfate content of blood is often greatly increased in chronic nephritis with nitrogen retention. More recently Atchley (10) found that, after complete ablation of kidney function, both  $\text{PO}_4$  and  $\text{SO}_4$  accumulated in the serum and that the increases of these two ions accounted for the reduction of the concentrations of  $\text{HCO}_3$  and Cl. In the present work no attempt has been made to estimate  $\text{SO}_4$  directly. It is, however, included in the "undetermined acid" fraction. Figure 1 D, while proving that excessive  $\text{PO}_4$  + undetermined acid values occur, also shows that the increases are far less frequent and usually of smaller magnitude than  $\text{CO}_2$  reductions. This would prove, as far as statistical treatment can prove, that accumulation of inorganic phosphate, sulfur, organic acids or any combination of the three affords an entirely unsatisfactory explanation of nephritic acidosis as a whole, although any one of them exist and act as a contributory factor in individual instances. Figure 2 more specifically demonstrates the absence of any definite relation between  $\text{PO}_4$ , undetermined acid and  $\text{HCO}_3$  in observations in which all were determined.

Analysis of data from individual cases shows that high undetermined acid occurred, with few exceptions, only when vomiting was an important symptom and on this account or another patients had not received adequate carbohydrate and fluids by mouth or by parenteral routes. It was more frequently encountered in the cases observed early in the study when the administration of carbohydrate fluids was not so vigorously pushed, it often failed to appear even in the premortal state when large amounts of carbohydrate and fluid were given, and it often disappeared rapidly after their administration.

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Even if accumulation of phosphate and sulfate in the blood were responsible for or regularly associated with the observed bicarbonate reductions, it would still be impossible to ascribe the phosphate and sulfate accumulations directly to failure of the renal excretory function. Such an explanation involves certain assumptions that phosphates and sulfates are obligatory excretory products for the elimination of which the organism is dependent upon the kidney, and that, in advanced renal disease, the urinary excretion of these substances is diminished. As far as phosphate is concerned, neither of these assumptions is supported by experimental work. Phosphate is largely excreted in the feces as well as the urine and its partition between feces and urine seems to be determined chiefly according to the needs of the organism for the elimination of acids or bases. Its level in the blood can be altered without appreciable effect on its excretion in the urine (12) and its elimination by the kidneys can be completely or almost checked by procedures that have no demonstrable injurious effects upon the kidneys (13). Even if it were granted that the phosphate accumulations in the serum of dogs after complete ablation of kidney function demonstrated by Atchley (10) were a direct result of the animals' inability to excrete phosphorus in the urine, it remains doubtful whether such extreme experiments have any important bearing on the problem of clinical nephritis. The deduction that similar accumulations observed in dogs after pyloric obstruction are due to renal injury (14) seems unwarranted.

Boyd (15) found that nephritic children with high serum phosphate showed negative phosphate balances on diets containing small, but adequate amounts of phosphorus. One experiment performed by Fetter (16) has an interesting bearing on the whole problem of the relation of hyperphosphatemia to acidosis and renal function in nephritis. Fetter administered disodium phosphate to a nephritic patient with high serum phosphate and low bicarbonate. As a result serum bicarbonate was restored to the normal level and urinary phosphate increased, but serum phosphate remained unchanged.

Because of the low concentration of sulfate in normal blood and the rapidity with which administered sulfate is excreted in the urine, it is generally assumed with some reason that sulfate is essentially a waste product and an obligatory excretory product for the elimination of

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As to the causes for high base concentration the data available are altogether too meager to permit any entirely satisfactory conclusions. High base occurred only when patients were or had recently been outside of the hospital on comparatively unregulated diets. In one case, 33247, administration of large amounts of fluid, with the production of water diuresis without salt restriction, was followed by reduction of the base concentration to the normal level within a week. One gains the impression that the insufficient kidney is unable to excrete large quantities of base unless large amounts of water are simultaneously made available.

Low base is encountered far more frequently than high base and is especially prone to develop in the uremic state. As base may be considered a measure of the total electrolyte concentration of the serum, it is also a measure of the substances normally responsible for the determination and maintenance of the osmotic pressure of the serum. On this account it has been suggested that the total electrolyte (base) deficiency in the serum in nephritis is an adaptive reaction to compensate for the presence of an abnormal excess of organic molecules, such as the end products of nitrogenous metabolism, which accumulate in the blood as the result of renal insufficiency. Gram (17) and others have, in point of fact, demonstrated, in certain cases of nephritis with nitrogen retention, diminished serum conductivity with normal or excessive freezing point depressions. A similar association of high non-protein nitrogen and low base is found in pyloric obstruction. Because, from the nature of the condition, it seems logical to presume that the reduction of base is the primary change, Hartmann, Scott and Moser (18) have sug-

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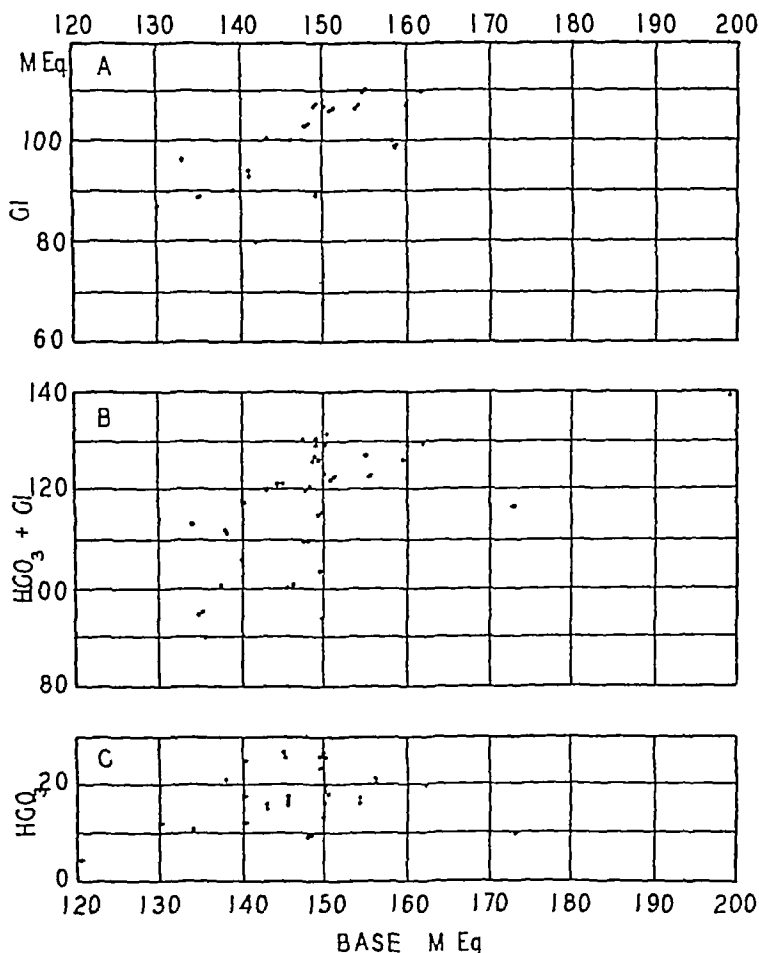


FIG 4 Cl, HCO<sub>3</sub> + Cl AND HCO<sub>3</sub> PLOTTED AGAINST BASE

were both frequent but unconnected results of the same pathologic condition. Theoretically it is questionable whether a reduction of electrolytes to which body membranes show a peculiarly selective permeability would offer an effective compensation for increased

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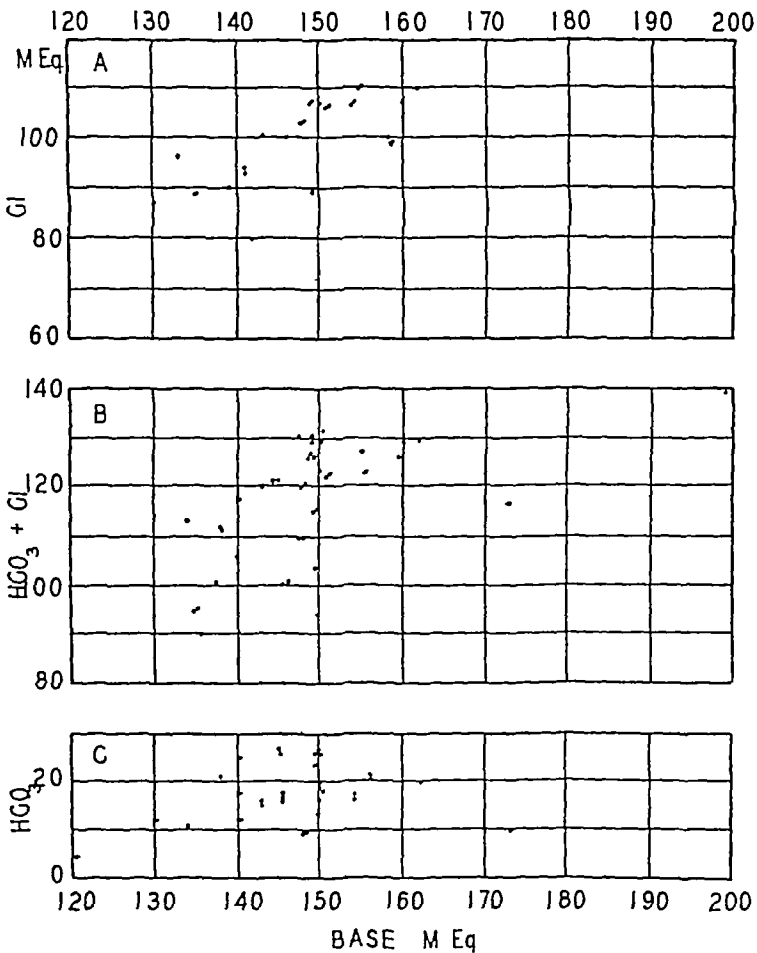


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If the determinations with high base only are considered it appears that the acids that combine with the excess are Cl or undetermined acids. Among the cases with low or normal base one finds a few in which Cl is above the normal level with  $\text{HCO}_3$  proportionately reduced. Both these groups conform to the type which Blum, Delaville and Van Caulaert (21) and others have spoken of as "dry chloride retention." Such a term, however, carries the unproved implication that the hyperchloremia is a primary change, the result of inability of the kidney to excrete the chloride ion.

In most cases in which Cl is low, base is also diminished, the converse is not, however, as consistently true.  $\text{HCO}_3$ , alone may bear the brunt of base reduction.

It is evident that most of the disturbances described can be included under the general term "acidosis," if the latter is used in the sense in which Van Slyke has employed it to describe those conditions in which there is a deficiency of bicarbonate (or base not bound by acids other than carbonic). It is clear, however, that such a simple term hardly does justice to the great variety of electrolyte patterns observed in nephritis. Such reductions of bicarbonate may be associated with total electrolyte deficiency (low total base), high Cl, high phosphate, high undetermined acid, or a combination of two or more of these factors. It is also clear that profound disturbances of electrolyte equilibrium may occur without any serious alteration of bicarbonate, especially if base is high. It would seem obvious that more than one factor must be responsible for the production of so many diverse patterns and that, to be rational, therapy must take these factors into account.

#### *Pathogenesis of electrolyte changes and their therapeutic implications*

In discussing the subject of pathogenesis of electrolyte change and their therapeutic implications use will be made of certain metabolism data which are presented in the succeeding paper. In the last column of Table 3 when it is noted that the Cl-balance was negative it means that the Cl in the excreta collected exceeded that in the food and

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In discussing the subject of pathogenesis of electrolyte change and their therapeutic implications use will be made of certain metabolism data which are presented in the succeeding paper. In the last column of Table 3 when it is noted that the Cl-balance was negative it means that the Cl in the excreta collected exceeded that in the food and

spite of the fact that both Cl and  $\text{PO}_4$  + undetermined acid are often elevated. This explains the fact that  $\text{HCO}_3$  never exceeds the normal limits.

If the determinations with high base only are considered it appears that the acids that combine with the excess are Cl or undetermined acids. Among the cases with low or normal base one finds a few in which Cl is above the normal level with  $\text{HCO}_3$  proportionately reduced. Both these groups conform to the type which Blum, Delaville and Van Caulaert (21) and others have spoken of as "dry chloride retention." Such a term, however, carries the unproved implication that the hyperchloremia is a primary change, the result of inability of the kidney to excrete the chloride ion.

In most cases in which Cl is low, base is also diminished, the converse is not, however, as consistently true.  $\text{HCO}_3$ , alone may bear the brunt of base reduction.

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It has been suggested that the hypochloremia of nephritis is due to transfer of Cl from blood and body fluids to the tissues, where it accumulates in excess. In dogs deprived of kidney function Atchley (10) was unable to detect such accumulations in any tissues which he analyzed. In our own studies, when all excreta were collected and analyzed it proved possible to account for changes in the level of serum Cl from observed salt and water balances. There would seem to be, in the most severe stages of nephritis with uremia, a loss of the ability of the organism to maintain the usual equilibrium between salt and water excretion and to maintain the concentration of these substances in the serum at the normal constant level. Cl continues to appear in the urine in relatively large amounts even when serum Cl has fallen far below the normal level and even below the level which has been called by Ambard the threshold of chloride excretion.

On the other hand, by giving large amounts of salt, it is possible to maintain Cl at the normal level or to restore it if it is reduced. It is even possible to push it above normal, especially if the fluid intake is not increased in proportion to the salt. Apparently the ability to eliminate large amounts of salt, especially in the absence of a proportional amount of water available for urine formation, is impaired.

In general serum base concentration follows that of Cl, although there are distinct exceptions to this rule. From this one can infer that chloride is largely excreted as BCl. Unfortunately, because of technical difficulties, base balances have been determined in no cases. Base is often reduced when Cl is normal or high and is sometimes high in relation to Cl. These exceptions to the general rule of parallelism between these two factors are probably referable to the accumulation of other acids that may specifically depress Cl, on the one hand, and impairment of the mechanism for the formation of ammonia on the other. Because of the latter the organism is forced to employ fixed base to neutralize any acid products of metabolism excreted in the urine.

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with uremia, enough salt must also be given to prevent salt depletion. How much salt should be given is another question. The authors have found that in cases in which there is no tendency to waste salt by extrarenal channels, 7 to 10 grams of NaCl daily (that is, 5-7 grams added to a salt-poor diet) is sufficient, if the urine volume is 2000 to 3000 cc. If because of previous misdirected dietary therapy or restriction of fluids, dehydration or salt depletion or both already exist, larger amounts of salt are required at first to overcome deficiencies and to permit the retention and storage of water without dilution of the electrolytes of serum and tissues.

Undoubtedly such treatment will, at times, result in the production of or aggravate an already existing edema. In this series edema was never observed, even after the subcutaneous administration of large amounts of saline, unless there were present obvious signs or symptoms of heart failure. This is generally recognized to be the rule in these patients, who ordinarily have a definite tendency to diuresis. The aim of forcing fluids and salt is to overcome and prevent dehydration and to promote the elimination of a large urine volume. Obviously, in the presence of heart failure, oliguria and edema, this end can not be effected unless cardiac compensation can be established. However, fluid restriction even in these cases should be moderate and can only be considered as a temporary expedient. Metabolism does not cease and the production of metabolites, the retention of which is the presumable cause of uremia and death in these cases, continues whether urine is excreted or not, with the result that these substances accumulate in excess in the body during periods of oliguria. The only salvation for such patients is the elimination of an adequate urine volume. Unless this can be induced by rest and digitalis a fatal outcome is inevitable.

The large amounts of fluid lost by extrarenal channels are often forgotten in the treatment of these cases. Loss of water by lungs, sweat, vomitus and bowel is of little benefit to the organism in the elimination of metabolic products. That this is becoming more and more generally accepted theory is evidenced by the ever diminishing use of so-called "depleting measures." In nephritis with edema from heart failure dyspnea is a striking feature, often the result of fixed acidosis as well as of the factors active in the production of cardiac

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In certain instances, then, base reductions develop in excess of Cl deficit, perhaps because base is wasted in the urine for the neutralization of foreign acids, since ammonia is unavailable. Under these circumstances bicarbonate administration is indicated. It is not, however, rational to attempt to restore base deficiency in general, or low  $\text{CO}_2$  capacity due to other causes, by bicarbonate therapy. Ellis (22) has pointed out the tendency of nephritic patients to develop alkalosis and tetany, if they are given bicarbonate when it is not clearly indicated.

A word should, perhaps, be said about the serum proteins in relation to acid-base equilibrium, although the general subject of the proteins in renal disease will be treated in a separate publication. The concentration of serum proteins is extremely variable, but more often low than high and, therefore, can not be held responsible for reductions of  $\text{HCO}_3$  or Cl. The rapid variability of the proteins suggests changes in the water content of the blood.

#### SUMMARY

Studies of the total electrolyte equilibrium of the serum have been made on a large series of patients with serious renal damage due to nephritis, vascular disease and "surgical" kidney conditions.

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The most prominent feature of the data is the extreme variability of almost every electrolyte component.

On admission he appeared pale, wasted, dehydrated, somewhat stuporous, breathing rapidly and heavily, with face and extremities twitching. His heart was enlarged, his systolic blood pressure 180, diastolic 115. He had advanced albuminuric retinitis.

Administration of adequate calories and fluids by mouth failed because of continuous vomiting. His stupor deepened to coma and he finally developed convulsions.

At the time of the 14th study, December 17th, he was much improved, rational, and taking food and fluids by mouth without vomiting. December 22nd, he was able to sit up in a chair.

December 24th he was seized with pain in the flanks, urgency and dysuria, and pus was found in his urine. After this he became rapidly worse.

At the time of the last examination, January 9th, he was again stuporous and vomiting. His breathing was labored and stertorous and profuse râles were heard over both lungs. He died January 11th.

The urine showed a specific gravity constantly low, 1.002 — 1.010, a variable amount of albumin, casts and red cells. After December 24th, 1925 it became frankly purulent.

He had a progressive anemia, his red blood cells and hemoglobin falling from 4.7 million and 80 per cent, respectively, to 1.5 million and 45 per cent in the course of his disease.

Autopsy revealed scars of kidney with glomerular adhesions and atrophy and hypertrophy of tubules. Subsidiary: Cardiac hypertrophy. Fibrosis of myocardium. Focal pneumonia. Arteriosclerosis. Acute cystitis.

*Case no 60345* A married American woman, aged 21, was admitted to the hospital April 16, 1927.

During the preceding year she had developed increasingly frequent headaches, dyspnea on exertion, cardiac palpitation, polyuria and nocturia. Very recently puffiness of the face, swelling of her legs, pain and swelling of her throat had appeared, attended by a racking non-productive cough, diffuse backache and dull headache, and later vomiting. As the vomiting increased the edema diminished, but other symptoms, including dyspnea, became aggravated.

She appeared acutely ill, anxious and distressed, pale, cyanotic, with marked dyspnea and orthopnea, tachycardia and a blood pressure of 180/120. There was some puffiness about the eyes, extremities and trunk, but no definite edema. The heart was much enlarged, with a rough systolic murmur at the apex and accentuation of the aortic second sound. Over the bases of both lungs there were dullness and numerous râles, especially on the left side where the breath sounds were somewhat suppressed. The liver was large and tender. There were no significant retinal changes.

With rest, digitalis, and dietetic treatment she improved greatly and was discharged on June 26th. She was readmitted August 31st, in a stuporous condition.

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At the time of the second study the arthritis was subsiding. By May 6th, when he was free from arthritis, the blood non-protein nitrogen had fallen to 58 mgm per 100 cc. He was discharged in this condition, greatly improved.

The third examination was made May 28th, when he returned to the dispensary in another acute attack of arthritis. He did not return again.

His urine showed a specific gravity of 1.005 to 1.012. At first there was much albumin and many red blood cells, but these diminished as the acute attack of gout subsided.

Blood counts: 4.1 to 3.6 million red blood cells, 85 to 60 per cent hemoglobin, 17,200 to 4,900 leucocytes.

*Case no. 36041* A single male, aged 29, was admitted to the hospital February 23, 1925.

He was reported to have had acute nephritis in 1909, and after 1918 albumin and casts were repeatedly found in his urine. February 23, 1925, his blood pressure was 172/115, but it fell to 142/110 by March 4th when he was discharged. Physical examination was otherwise negative except for a small tophus on the right ear, and the patient was free from all symptoms.

In August 1925, he had an acute attack of gout lasting four or five days and relieved by cinchophen.

From April 1925 on he complained of more and more persistent suboccipital headaches, which continued in spite of medication. His systolic blood pressure also remained more consistently high and the diastolic pressure rose.

October 15th, 1926 the blood was examined again because of the persistent headache and he was ordered a diet restricted in both protein and salt. The fourth blood study was made November 12th, after he had been on this diet for almost a month. The fifth examination was made a month later when he had relaxed his diet. The third, fourth and fifth were all made while the patient was out of the hospital and the diets were never strictly controlled. The changes in dietary salt did not influence his symptoms.

His condition continued with little change until May 1927, when he began to complain of occasional cardiac palpitation. During the succeeding summer he went away for a month's vacation and, during this, was somewhat relieved of his headaches and other symptoms. However, they recurred as soon as he resumed his normal life.

After the latter part of December 1927, he had increasingly frequent attacks of cardiac palpitation and dyspnea. In March 1928, he also developed anorexia and nausea, with occasional vomiting.

April 7th he began to vomit at frequent intervals and the following day developed arthritis of the left great toe. His breathlessness and headache had, meanwhile, improved. The arthritic pain was rapidly relieved by cinchophen, but vomiting continued. About two weeks later he developed a cough and his dyspnea returned.

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After this he was unable to take fluids, became more and more stuporous and, by March 8th, when the first blood examination was done, was in coma, with deep, labored respirations.

Intravenous glucose was given with some benefit on this day and on the next intravenous glucose and subcutaneous salt and glucose. The second study was made on March 10th, after this treatment. The treatment was repeated on the 10th, and on the 11th and 12th intravenous sodium bicarbonate was given as well. By March 11th he was much improved, conscious and able to take fluids by mouth. The third study was made on the 13th, after this treatment. After this, intravenous and subcutaneous treatments were stopped because he was able to take food by mouth. His salt and fluid intake fell somewhat lower, but he seemed relatively well when the last study was made, on March 19th and when he was discharged on March 21st. However, he died about three weeks later at home.

Autopsy was not obtained.

*Case no 20921* A married woman, aged 35, was admitted to the hospital February 26th, 1925.

In 1914, 1919 and 1922, the last time following a pregnancy, she had had cystitis and bilateral pyelitis.

February 22nd, 1925 she developed dizziness and blurring of vision, vomited, and felt feverish and weak. Three days later she "fainted" several times. February 28th severe headaches, dyspnea and palpitation began with extreme frequency of urination, thirst and vomiting. The next morning she had two convulsions for which she was sent to the hospital. On admission she appeared sick, anxious and restless and complained of severe occipital headache. Both optic discs were swollen and there were hemorrhages in both retinæ. The heart was not enlarged, the blood pressure was 200/150.

Her urine showed a specific gravity of 1.010, heavy albumin, numerous casts and leucocytes.

The first blood examination was done when she entered the hospital. She was given large amounts of carbohydrate containing fluids and salt for the first day and then a diet somewhat restricted in protein, but high in fluids and salt. She improved rapidly and by the time of the second study, March 9th, was eating her diet well and feeling quite fit. She was discharged on March 15th. After this she was followed in the Dispensary.

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The methods for control of diet and collection and analysis of excreta were only gradually developed as the work proceeded

In earlier studies salt poor diets or salt poor diets to which a known amount of salt had been added were given. The Cl in such salt poor diets, estimated by the aid of the usual tables of food composition never exceeded 35 mM (2 grams of NaCl) daily. Although low or falling serum Cl was usually attended by negative Cl-balances when patients were on salt poor diets, the addition of Cl to such diets sometimes resulted in positive Cl balances although serum Cl continued to fall. More rigid dietary control was therefore instituted.

All diets were prepared salt poor in the diet kitchen and their Cl-content carefully calculated from the best available food tables. Extra salt, carefully weighed, was provided in small flasks from the laboratory, to be added to the food during the day by the patient. Food refused by the patient was carefully reweighed, the salt and nitrogen in the refusals estimated and subtracted from the salt offered. The flasks were also reweighed in the laboratory at the end of the day if the extra salt had not all been used.

The decision to put added salt on the food in the wards was taken because it was appreciated that if such additions were made in the diet kitchen it was practically impossible to insure the complete transfer of the salt from cooking utensils to dishes, because such a technique required the separate preparation of each article of diet for every individual, and because it required separate weighing of the salt to be used on each individual dish in the diet. On the other hand, with the system adopted, if a patient was unable to eat any of the food he had salted it was impossible to estimate the amount of salt refused. As both appetites and digestions of some of these patients were most capricious, such occurrences were not uncommon. If salt thus lost were neglected apparent positive balances would result. When salt was given subcutaneously or intravenously, as it was in some of the most severe cases, salt intake could be calculated with considerable accuracy.

At first urine alone, collected with all the usual precautions, was analyzed for nitrogen and Cl. Attempts were also made to collect all vomitus, with only partial success. In later experiments great efforts were made to collect all excreta, urine, vomitus and feces.

Special urinals and bed-pans were provided by the laboratories to the wards. All specimens of urine, vomitus or feces were brought to the laboratory and placed immediately in the refrigerator in the receptacles in which they were originally collected. In the laboratory these specimens were quantitatively transferred, measured and subjected to analysis. If the stools were contaminated by urine, a surprisingly common occurrence considering the precautions taken against it, the urine was decanted and treated with the other urine.

Urine, feces, and vomitus were analyzed for both nitrogen and chloride. Urinary nitrogen was determined by the usual Kjeldahl procedure, Cl by Volhard-Harvey titration. In some of the earlier studies of vomitus Cl was determined in the same manner, while total and free acid were titrated with phenolphthalein and

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TABLE 1  
*Patients with hypochloremia*

| Number | Date        | Serum |       | Vomit |  |
|--------|-------------|-------|-------|-------|--|
|        |             | Cl    | Base  |       |  |
|        |             | mM    | mM    |       |  |
| 26672  |             | 74.6  |       | ++    | Urinary retention  |
| 14188  | December 9  | 127.1 |       | +     |  |
|        | December 16 | 78.6  |       | +     | Water without salt   |
| 18826  |             | 80.7  |       | +     |  |
| 26555  | December 10 | 95.1  |       | +     |  |
|        | December 12 | 90.1  |       | ++    |  |
| 29522  | March 6     | 91.8  |       | ++    | Urine contained little salt, but patient received practically none |
|        | March 17    | 89.6  |       | ++    |  |
|        | April 1     | 92.6  |       | ++    |  |
| 29039  | January 25  | 109.5 |       | +     | On admission   |
|        | January 26  | 88.6  |       |       | After fluids, including subcutaneous saline                        |
|        | January 27  | 97.4  |       |       | After bicarbonate, saline and glucose                              |
|        | January 28  | 98.5  |       |       | After further glucose and saline                                   |
| 33049  | April 26    | 86.8  |       | +     |  |
|        | April 30    | 86.8  |       |       | Fluids without salt  |
| 26409  | November 20 | 82.9  |       | ++    |  |
|        | November 28 | 82.9  |       |       | After salt poor diet. Negative Cl balance from urine alone         |
|        | December 5  | 87.5  |       | +     | After 7 days with low fluids and 7 grams of extra salt             |
|        | December 17 | 81.9  |       | +     | After 2 days of salt poor diet with high fluids                    |
|        | December 27 | 78.1  |       | +     | 2 days before death Stuporous, taking no fluids                    |
| 15012  | December 5  | 106.1 |       | 0     | On admission   |
|        | December 22 | 90.4  |       | 0     | After salt poor diet with forced fluids                            |
|        | January 20  | 103.7 |       | 0     | Records inadequate   |
| 28049  | February 8  | 89.2  |       | (+)   |  |
|        | February 11 | 80.4  |       | (+)   | Salt poor diet, high fluids Negative Cl balance                    |
|        | February 16 | 86.9  |       | +     | Negative Cl balance  |
|        | February 25 | 87.4  |       |       | Negative Cl balance  |
|        | March 1     | 87.2  |       | +     | Negative Cl balance  |
|        | March 4     | 93.0  |       |       | Subcutaneous saline on March 2 and 3                               |
|        | March 7     | 87.2  |       |       | Deep stupor  |
|        | March 8     | 89.9  |       |       | 12 hours before death } Taking no food, fluids nor salt            |
| 35795  |             | 92.2  | 146.3 | ++    | On admission   |
| 52843  | October 11  | 99.8  | 146.3 | +     |  |
|        | October 20  | 93.9  | 142.2 | +     | Vomited until October 17 and took little food, fluids or salt      |

TABLE 1  
*Patients with hypochloremia*

| Number | Date        | Serum |       | Vomit |  |
|--------|-------------|-------|-------|-------|--|
|        |             | Cl    | Base  |       |  |
|        |             | mM    | mM    |       |  |
| 26672  |             | 74 6  |       | ++    | Urinary retention  |
| 14188  | December 9  | 127 1 |       | +     |  |
|        | December 16 | 78 6  |       | +     | Water without salt   |
| 18826  |             | 80 7  |       | +     |  |
| 26555  | December 10 | 95 1  |       | +     |  |
|        | December 12 | 90 1  |       | ++    |  |
| 29522  | March 6     | 91 8  |       | ++    | Urine contained little salt, but patient received practically none |
|        | March 17    | 89 6  |       | ++    |  |
|        | April 1     | 92 6  |       | ++    |  |
| 29039  | January 25  | 109 5 |       | +     | On admission   |
|        | January 26  | 88 6  |       |       | After fluids, including subcutaneous saline                        |
|        | January 27  | 97 4  |       |       | After bicarbonate, saline and glucose                              |
|        | January 28  | 98 5  |       |       | After further glucose and saline                                   |
| 33049  | April 26    | 86 8  |       | +     |  |
|        | April 30    | 86 8  |       |       | Fluids without salt  |
| 26409  | November 20 | 82 9  |       | ++    |  |
|        | November 28 | 82 9  |       |       | After salt poor diet. Negative Cl balance from urine alone         |
|        | December 5  | 87 5  |       | +     | After 7 days with low fluids and 7 grams of extra salt             |
|        | December 17 | 81 9  |       | +     | After 2 days of salt poor diet with high fluids                    |
|        | December 27 | 78 1  |       | +     | 2 days before death Stuporous, taking no fluids                    |
| 15012  | December 5  | 106 1 |       | 0     | On admission   |
|        | December 22 | 90 4  |       | 0     | After salt poor diet with forced fluids                            |
|        | January 20  | 103 7 |       | 0     | Records inadequate   |
| 28049  | February 8  | 89 2  |       | (+)   |  |
|        | February 11 | 80 4  |       | (+)   | Salt poor diet, high fluids Negative Cl balance                    |
|        | February 16 | 86 9  |       | +     | Negative Cl balance  |
|        | February 25 | 87 4  |       |       | Negative Cl balance  |
|        | March 1     | 87 2  |       | +     | Negative Cl balance  |
|        | March 4     | 93 0  |       |       | Subcutaneous saline on March 2 and 3                               |
|        | March 7     | 87 2  |       |       | Deep stupor  |
|        | March 8     | 89 9  |       |       | 12 hours before death } Taking no food, fluids nor salt            |
| 35795  |             | 92 2  | 146 3 | ++    | On admission   |
| 52843  | October 11  | 99 8  | 146 3 | +     |  |
|        | October 20  | 93 9  | 142 2 | +     | Vomited until October 17 and took little food, fluids or salt      |



foods was contemplated, but was not adopted. Such diets would have been highly desirable from the standpoint of securing superior data, but, from the standpoint of therapy and the happiness of the experimental subjects, would have been less satisfactory than the diets actually given, which were chosen with attention to the tastes and caprices of the patients and with careful consideration of existing psychological and physiological disturbances of appetite, digestion and other functions.

Examination of table 1 shows that in 25 out of 63 instances low serum Cl was observed in patients who had, during a preceding period, received little or no salt, either because they had been given salt poor diets or because, on account of coma, stupor or vomiting, they had been unwilling or unable to take diet or fluids. Besides this in every one of the 16 examinations in which hypochloremia was found at the time of admission to hospital persistent vomiting had been an outstanding symptom. In three other instances Cl balances had been distinctly negative. In still another three, Cl was still low, but had risen from a previous lower level in response to the administration of sufficient salt to produce a positive balance. Data are inadequate for the analysis of four determinations. On three occasions bicarbonate had been given. Twice edema appeared to explain the coexistence of hypochloremia and a positive Cl balance.

This leaves only 7 out of 63 instances in which, while patients were in the hospital, reduction of Cl, which could not be explained on the basis of relative dietary deficiency, persisted.

Vomiting, which was a prominent feature in 55 of the total 77 and in 48 of the 63 hypochloremic observations, offers the most obvious explanation for the deficits of Cl and base. It was, however, entirely lacking on 7 of the 15 occasions when low Cl followed or was associated with insufficient salt intake.

It has generally been held, with much experimental support, that it is impossible by limiting salt intake to reduce significantly the chloride concentration of the serum of normal individuals, even if high fluids are given unless, at the same time, Cl loss by extrarenal channels is augmented. The normal kidneys appear to offer an effectual bar to chloride depletion. Furthermore, if chloride loss by other channels is increased as, for instance, in pyloric obstruction,

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TABLE 2—Continued

| Case number | Date        | Serum Cl | Urine volume | Urine Cl     |            |             |
|-------------|-------------|----------|--------------|--------------|------------|-------------|
|             |             |          |              | mM per liter | mM per day |             |
| 29522       | 1924        | mM       | cc           |              |            | Involuntary |
|             | March 6     | 91 8     | 360          | 16           | 6          |             |
|             | March 16    |          | 1,280        | 24           | 31         |             |
|             | March 17    | 89 6     | 1,080        | 21           | 22         |             |
| 29267       | April 1     | 92 6     | 380          | 33           | 11         |             |
|             | 1925        |          |              |              |            |             |
|             | November 26 |          | 2,520        | 41           | 10         |             |
|             | November 27 | 96 4     | 2,800        | 40           | 11         |             |
|             | November 30 |          | 1,270+       | 39           | 50+        |             |
|             | December 1  | 95 3     | 1,770        | 42           | 74         |             |
| 56247       | December 5  |          | 950          | 164          | 156        |             |
|             | December 6  | 96 2     | 520          | 263          | 137        |             |
|             | 1926        |          |              |              |            |             |
|             | January 1   |          | 2,860        | 44           | 125        |             |
|             | January 2   | 94 4     |              |              |            |             |
|             | January 17  |          | 1,560        | 18           | 27         |             |
|             | January 18  | 94 7     | 1,500        | 30           | 44         |             |
|             | January 24  |          | 1,500        | 24           | 36         |             |
|             | January 25  | 92 5     | 1,560        | 19           | 29         |             |
|             | January 31  |          | 1,390        | 21           | 29         |             |
| 29635       | February 1  | 87 0     | 1,390        | 21           | 29         |             |
|             | April 17    |          | 1,970        | 18           | 26         |             |
| 18496       | April 18    | 88 8     |              |              |            |             |
|             | June 2      | 95 0     |              |              |            |             |
| 22684       | 1923        |          |              |              |            |             |
|             | December 13 | 93 7     | 370          | 33           | 12         |             |
|             | December 18 |          | 1,950        | 100          | 195        |             |
|             | December 19 | 90 3     | 800          | 15           | 12         |             |
|             | December 30 |          | 325          | 5            | 2          |             |
|             | December 31 | 75 4     | 540          | 8            | 4          |             |
| 29796       | 1924        |          |              |              |            |             |
|             | April 7     | 93 7     | 580          | 30           | 17         |             |
| 18925       | 1923        |          |              |              |            |             |
|             | June 15     | 94 4     |              |              |            |             |
|             | June 18     |          |              | 59           |            |             |
|             | June 20     | 78 1     |              | 64           |            |             |

urine Cl diminishes rapidly to vanish, finally, when serum Cl has fallen to a certain minimum level Ambard (4) claims that Cl disappears from the urine when its concentration in the serum drops below 96 milliequivalents (5.62 grams per liter) In a series of

TABLE 2—Continued

| Case number | Date        | Serum Cl | Urine volume | Urine Cl     |            |             |
|-------------|-------------|----------|--------------|--------------|------------|-------------|
|             |             | mM       | cc           | mM per liter | mM per day |             |
| 29522       | 1924        |          |              |              |            |             |
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|             | April 1     | 92 6     | 380          | 33           | 11         |             |
| 29267       | 1925        |          |              |              |            |             |
|             | November 26 |          | 2,520        | 41           | 10         |             |
|             | November 27 | 96 4     | 2,800        | 40           | 11         |             |
|             | November 30 |          | 1,270+       | 39           | 50+        |             |
|             | December 1  | 95 3     | 1,770        | 42           | 74         |             |
|             | December 5  |          | 950          | 164          | 156        |             |
|             | December 6  | 96 2     | 520          | 263          | 137        |             |
| 56247       | 1926        |          |              |              |            |             |
|             | January 1   |          | 2,860        | 44           | 125        | Involuntary |
|             | January 2   | 94 4     |              |              |            |             |
|             | January 17  |          | 1,560        | 18           | 27         |             |
|             | January 18  | 94 7     | 1,500        | 30           | 44         |             |
|             | January 24  |          | 1,500        | 24           | 36         |             |
|             | January 25  | 92 5     | 1,560        | 19           | 29         |             |
|             | January 31  |          | 1,390        | 21           | 29         |             |
|             | February 1  | 87 0     | 1,390        | 21           | 29         |             |
|             | 29635       | April 17 |              | 1,970        | 18         |             |
|             | April 18    | 88 8     |              |              |            |             |
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| 22684       | 1923        |          |              |              |            |             |
|             | December 13 | 93 7     | 370          | 33           | 12         |             |
|             | December 18 |          | 1,950        | 100          | 195        |             |
|             | December 19 | 90 3     | 800          | 15           | 12         |             |
|             | December 30 |          | 325          | 5            | 2          |             |
|             | December 31 | 75 4     | 540          | 8            | 4          |             |
| 29796       | 1924        |          |              |              |            |             |
|             | April 7     | 93 7     | 580          | 30           | 17         |             |
| 18925       | 1923        |          |              |              |            |             |
|             | June 15     | 94 4     |              |              |            |             |
|             | June 18     |          |              | 59           |            |             |
|             | June 20     | 78 1     |              | 64           |            |             |

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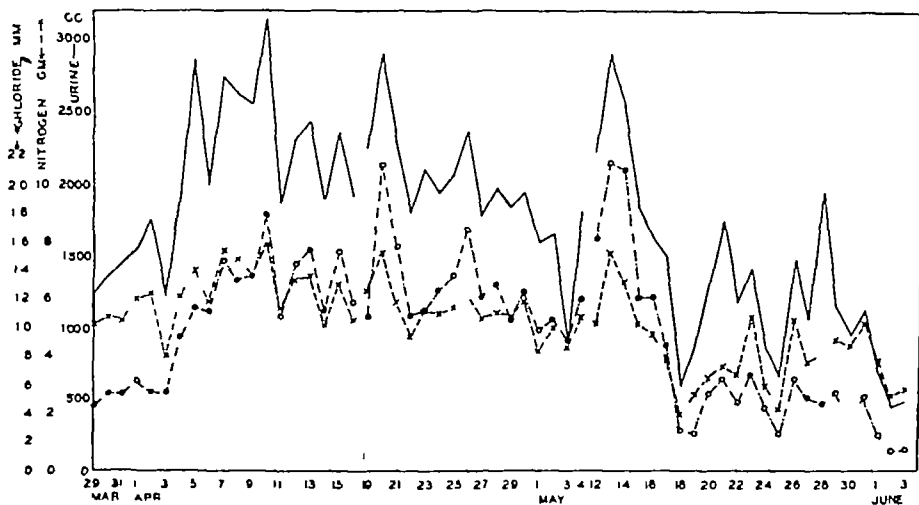


FIG 1 CASE 20921

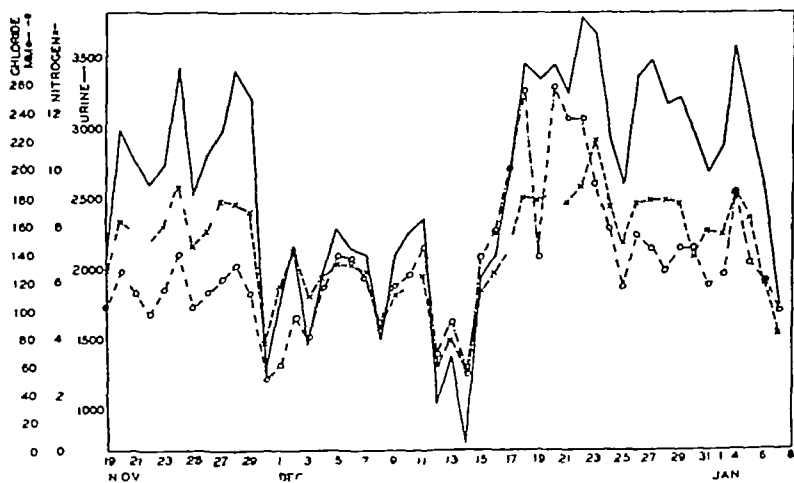


FIG 2 CASE 29267

solution of the same molecular concentration as blood serum. This fixation of concentration is supposed to be exhibited in the excretion

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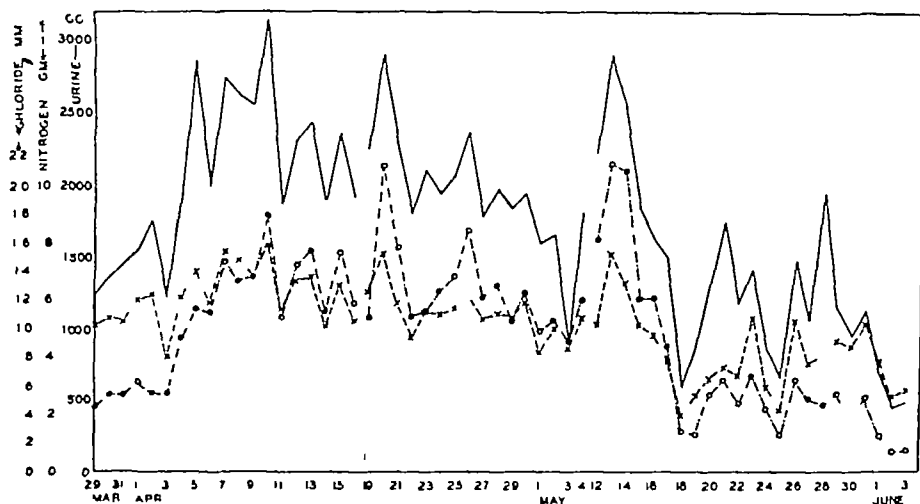


FIG 1 CASE 20921

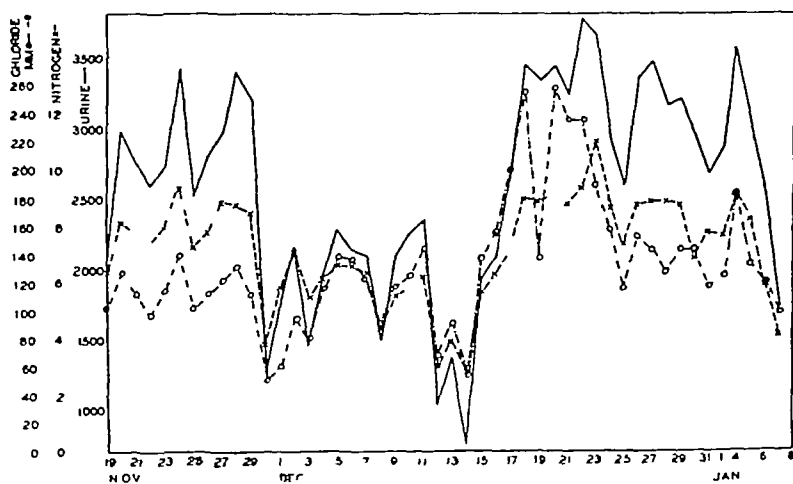


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solution of the same molecular concentration as blood serum. This fixation of concentration is supposed to be exhibited in the excretion

long periods, although it is relatively fixed over shorter intervals. Comparison with the level of serum chloride also reveals no close relation with either concentration or total amount of chloride in urine. To be sure both rise considerably when the serum chloride is pushed up by the administration of large amounts of chloride as, for example, in the middle period of figure 3. On the other hand at the end of the course of study of this case both total excretion and concentration were at almost the same level as they were at the beginning, although serum Cl had fallen from 100.5 to 91.6 mM.

It is, apparently, possible to elevate the concentration of chloride in serum and in urine and to augment its excretion by the administration of sufficiently large amounts of salt. On the other hand, water and chloride excretion seem to be more dependent upon one another than normal under any given conditions, as is evidenced by the rough parallelism between them in the charts. Furthermore, chloride continues to be eliminated at a rather constant rate at levels of serum Cl that usually result in achloruria. Finally, in no case studied did even the most vigorous administration of salt lead to the elimination of a urine of high salt concentration even if serum Cl was driven far above the normal level. In fact only on two or three isolated occasions on single days in different patients did the urine chloride concentration equal that of the nearest serum observations. In these instances it is quite possible that serum chlorides were higher at the time of passage of the concentrated urine than they had been when the blood was withdrawn for analysis.

There is, then, an evident tendency to hyposthenuria and isosthenuria for Cl, although it is possible to cause considerable variation in the concentration of Cl below a certain level. The data suggest that the limit of concentrating power is the concentration of Cl in the serum.

If there is a definite hyposthenuric tendency, administration of either salt or water, within the capacity of the organism, should facilitate the excretion of the other. If there is any tendency at normal or high levels of Cl for salt excretion to be accelerated and for diuresis to occur, it would seem advisable to adopt measures to promote such a process. If, even at low levels of Cl ingestion and of serum chloride, excretion continues and is facilitated by water diuresis, administration

long periods, although it is relatively fixed over shorter intervals. Comparison with the level of serum chloride also reveals no close relation with either concentration or total amount of chloride in urine. To be sure both rise considerably when the serum chloride is pushed up by the administration of large amounts of chloride as, for example, in the middle period of figure 3. On the other hand at the end of the course of study of this case both total excretion and concentration were at almost the same level as they were at the beginning, although serum Cl had fallen from 100.5 to 91.6 mM.

It is, apparently, possible to elevate the concentration of chloride in serum and in urine and to augment its excretion by the administration of sufficiently large amounts of salt. On the other hand, water and chloride excretion seem to be more dependent upon one another than normal under any given conditions, as is evidenced by the rough parallelism between them in the charts. Furthermore, chloride continues to be eliminated at a rather constant rate at levels of serum Cl that usually result in achloruria. Finally, in no case studied did even the most vigorous administration of salt lead to the elimination of a urine of high salt concentration even if serum Cl was driven far above the normal level. In fact only on two or three isolated occasions on single days in different patients did the urine chloride concentration equal that of the nearest serum observations. In these instances it is quite possible that serum chlorides were higher at the time of passage of the concentrated urine than they had been when the blood was withdrawn for analysis.

There is, then, an evident tendency to hyposthenuria and isosthenuria for Cl, although it is possible to cause considerable variation in the concentration of Cl below a certain level. The data suggest that the limit of concentrating power is the concentration of Cl in the serum.

If there is a definite hyposthenuric tendency, administration of either salt or water, within the capacity of the organism, should facilitate the excretion of the other. If there is any tendency at normal or high levels of Cl for salt excretion to be accelerated and for diuresis to occur, it would seem advisable to adopt measures to promote such a process. If, even at low levels of Cl ingestion and of serum chloride, excretion continues and is facilitated by water diuresis, administration



usually far in excess of that in vomitus. In another sense vomiting is by no means a negligible factor in the production of hypochloremia. When vomiting seriously interferes with the ingestion of adequate amounts of food and fluids, the salt intake becomes of necessity limited and chloride wastage through the kidneys ensues as it does when a salt-poor diet is given.

It is of some interest to note that hypochloremia does not have the same limiting influence on gastric Cl elimination as it does on urine chloride excretion. Cl may be excreted in relatively high concentration in vomitus when the urine has become almost chloride free. This is best illustrated by case 35805, tables 1 and 5. Studies of pyloric stenosis would lead us to expect these results. In most of the observations deductions concerning the concentrating powers of the stomach can not be drawn because it is uncertain how much of the Cl recovered was derived directly from recently ingested food. A few cases, especially 35805 and 56247 received nothing by mouth except occasionally salt-free carbohydrate fluids, all salt was given subcutaneously.

Analysis of both vomitus and urine still failed to account for all the salt lost from the serum in some cases, so examination of feces was undertaken. In most instances the amount of Cl in the stools was appreciable but not great and appeared to be due to the loss of urine during defecation, a frequently neglected factor that in these experiments has proved to be a source of large error. It is surprising how few patients, especially among women, can control the vesical and anal sphincters independently with any consistent measure of success. Case no. 56247, table 4, however, does show a loss of Cl in the stools so large that it can not be explained as due to urine. Whether similar leakage of chloride via the bowel is a common cause of salt loss in nephritics or only a peculiar anomaly of this individual remains to be determined when other subjects presenting similar conditions are observed. It at least offers a possible explanation of some hitherto inexplicable chloride deficiencies.

#### *Low serum base*

In general fluctuations of serum Cl are reflected in parallel variations of base, although there are exceptions to this rule, as has been indi-

usually far in excess of that in vomitús. In another sense vomiting is by no means a negligible factor in the production of hypochloremia. When vomiting seriously interferes with the ingestion of adequate amounts of food and fluids, the salt intake becomes of necessity limited and chloride wastage through the kidneys ensues as it does when a salt-poor diet is given.

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#### *Low serum base*

In general fluctuations of serum Cl are reflected in parallel variations of base, although there are exceptions to this rule, as has been indi-



TABLE 3  
Case no 29267

| Date        | Weight<br>kgm | Fluid        |              | Nitrogen        |                    |       | Cl           |                 |     | Urine      |              | Blood<br>N P N<br>mgm per<br>100 cc | Serum    |            |
|-------------|---------------|--------------|--------------|-----------------|--------------------|-------|--------------|-----------------|-----|------------|--------------|-------------------------------------|----------|------------|
|             |               | Intake<br>cc | Urine<br>cc. | Intake<br>grams | Urine              |       | Intake<br>mM | Urine           |     | Base<br>mM | B - Cl<br>mM |                                     | Cl<br>mM | Base<br>mM |
| 1925        |               |              |              |                 | grams<br>per liter | grams |              | mM<br>per liter | mM  |            |              |                                     |          |            |
| November 19 | 59 0          | 2,900        | 2,060        | 9 7             | 3 1                | 6 4   | 127          | 50              | 103 |            |              | 167                                 | 105 5    | 173 0      |
| November 20 |               | 3,500        | 2,980        | 9 8             | 2 8                | 8 2   | 128          | 43              | 128 | 178        | 50           |                                     |          |            |
| November 21 |               | 3,100        | 2,740        | 9 4             | 2 8                | 7 8   | 118          | 41              | 112 | 178        | 66           |                                     |          |            |
| November 22 |               | 3,400        | 2,600        | 9 6             | 2 8                | 7 4   | 142          | 38              | 98  | 164        | 66           |                                     |          |            |
| November 23 |               | 2,800        | 2,720        | 9 3             | 2 9                | 8 0   | 169          | 42              | 114 | 177        | 63           |                                     |          |            |
| November 24 | 58 8          | 4,750        | 3,420        | 8 2             | 2 7                | 9 4   | 147          | 41              | 140 | 196        | 56           | 160                                 |          |            |
| November 25 |               | 3,700        | 2,520        | 8 1             | 2 9                | 7 3   | 118          | 40              | 102 | 136        | 34           |                                     |          |            |
| November 26 |               | 4,900        | 2,800        | 7 1             | 2 8                | 7 8   | 118          | 40              | 112 | 154        | 42           |                                     |          |            |
| November 27 | 59 0          | 3,850        | 2,960        | 7 1             | 3 0                | 8 9   | 118          | 41              | 121 | 181        | 60           | 168                                 | 96 4     | 132 9      |
| November 28 |               | 3,900        | 3,400        | 7 4             | 2 6                | 8 8   | 113          | 39              | 131 | 175        | 44           |                                     |          |            |
| November 29 | 58 1          | 4,530        | 3,200        | 6 9             | 2 7                | 8 5   | 149          | 35              | 111 | 188        | 74           |                                     |          |            |
| November 30 |               | 3,950        | 1,270+       | 5 5             | 3 0                | 3 8+  | 309          | 39+             | 50+ |            |              |                                     |          |            |
| December 1  |               | 5,000        | 1,770        | 6 0             | 3 3                | 5 8   | 39           | 34              | 60  | 104        | 44           | 167                                 | 95 3     | 148 0      |
| December 2  |               | 2,230        | 2,170        | 0               | 3 3                | 7 1   | 53           | 44              | 96  | 155        | 59           |                                     |          |            |
| December 3  |               | 4,180        | 1,470        | 0               | 3 7                | 5 5   | 212          | 54              | 80  | 118        | 38           |                                     |          |            |
| December 4  |               | 2,880        | 1,950        | 5 1             | 3 2                | 6 2   | 75           | 59              | 116 | 164        | 48           |                                     |          |            |
| December 5  |               | 3,720        | 2,290        | 3 3             | 2 9                | 6 6   | 272          | 61              | 139 | 190        | 51           | 163                                 | 96 2     | 137 5      |
| December 6  |               | 4,550        | 2,040        | 0               | 3 2                | 6 6   | 282          | 67              | 137 | 192        | 55           |                                     |          |            |
| December 7  |               | 3,670        | 2,000        | 1 8             | 3 2                | 6 4   | 60           | 62              | 123 | 172        | 49           |                                     |          |            |

TABLE 4  
Case no 56247

| Period | Days | Fluid           |                 |             |             | Nitrogen    |        |               |           | Cl        |            |           |                | Initial |  |             |
|--------|------|-----------------|-----------------|-------------|-------------|-------------|--------|---------------|-----------|-----------|------------|-----------|----------------|---------|--|-------------|
|        |      | Intake          | Urine           | Food        | Urine       | Stools      | Vomit  | Balance       | Intake    | Urine     | Stools     | Vomit     | Balance        | Weight  | Blood<br>N P N<br>mgm<br>per<br>100 cc | Serum<br>Cl |
| II     | 7    | cc.             | cc              | grams       | grams       | grams       | grams  | grams         | mM        | mM        | mM         | mM        | mM             | kgm.    | mgm<br>per<br>100 cc                   | mM          |
|        |      | 16,130<br>2,300 | 11,530<br>1,650 | 56 6<br>8 1 | 53 0<br>7 6 | 21 6<br>3 1 | 0<br>0 | -12 0<br>-2 6 | 265<br>38 | 540<br>77 | 910<br>130 | 0<br>0    | -1,185<br>-169 | 61 6    | 77                                     | 99 2        |
| III    | 7    | 19,330<br>2,760 | 9,100<br>1,300  | 65 6<br>9 4 | 42 8<br>6 1 | 12 9<br>1 8 | 0<br>0 | -9 9<br>-1 4  | 327<br>46 | 253<br>36 | 503<br>72  | 3<br>0    | -433<br>-62    | 59 3    | 98                                     | 99 0        |
|        |      | 21,240<br>3,030 | 8,530<br>1,220  | 60 9<br>8 7 | 39 8<br>5 7 | 12 9<br>1 8 | 0<br>0 | -8 2<br>-1 2  | 301<br>26 | 320<br>31 | 503<br>72  | 0<br>0    | -422<br>-60    | 60 4    | 88                                     | 94 9        |
| V      | 8    | 28,280<br>3,540 | 14,630<br>1,830 | 12 4<br>1 6 | 42 2<br>5 3 | 3 7<br>0 5  |        | -33 5<br>-4 2 | 758<br>94 | 243<br>31 | 253<br>32  | 116<br>15 | 145<br>19      | 60 9    | 121                                    | 92 5        |

TABLE 4  
Case no 56247

| Period | Days | Fluid  |        | Nitrogen |       |        |       |         | Cl     |       |        |       | Initial |        |                      |             |
|--------|------|--------|--------|----------|-------|--------|-------|---------|--------|-------|--------|-------|---------|--------|----------------------|-------------|
|        |      | Intake | Urine  | Food     | Urine | Stools | Vomit | Balance | Intake | Urine | Stools | Vomit | Balance | Weight | Blood<br>N P N       | Serum<br>Cl |
|        |      | cc.    | cc     | grams    | grams | grams  | grams | grams   | mM     | mM    | mM     | mM    | mM      | kgm.   | mgm<br>per<br>100 cc | mM          |
| II     | 7 {  | 16,130 | 11,530 | 56 6     | 53 0  | 21 6   | 0     | -12 0   | 265    | 540   | 910    | 0     | -1,185  | 61 6   | 77                   | 99 2        |
|        |      | 2,300  | 1,650  | 8 1      | 7 6   | 3 1    | 0     | -2 6    | 38     | 77    | 130    | 0     | -169    |        |                      |             |
| III    | 7 {  | 19,330 | 9,100  | 65 6     | 42 8  | 12 9   | 0     | -9 9    | 327    | 253   | 503    | 3     | -433    | 59 3   | 98                   | 99 0        |
|        |      | 2,760  | 1,300  | 9 4      | 6 1   | 1 8    | 0     | -1 4    | 46     | 36    | 72     | 0     | -62     |        |                      |             |
| IV     | 7 {  | 21,240 | 8,530  | 60 9     | 39 8  | 12 9   | 0     | -8 2    | 301    | 320   | 503    | 0     | -422    | 60 4   | 88                   | 94 9        |
|        |      | 3,030  | 1,220  | 8 7      | 5 7   | 1 8    | 0     | -1 2    | 26     | 31    | 72     | 0     | -60     |        |                      |             |
| V      | 8 {  | 28,280 | 14,630 | 12 4     | 42 2  | 3 7    |       | -33 5   | 758    | 243   | 253    | 116   | 145     | 60 9   | 121                  | 92 5        |
|        |      | 3,540  | 1,830  | 1 6      | 5 3   | 0 5    |       | -4 2    | 94     | 31    | 32     | 15    | 19      |        |                      |             |

TABLE 5—Continued

| Case number | Date       | Urine   |              |     | Vomit  |              |      |              |               |              |            | Serum Cl |
|-------------|------------|---------|--------------|-----|--------|--------------|------|--------------|---------------|--------------|------------|----------|
|             |            | Vol ume |              | Cl  | Volume |              | Cl   |              | Free acid     |              | Total acid |          |
|             |            | cc      | mM per liter | mM  | cc     | mM per liter | mM   | mM per liter | mM            | mM per liter | mM         | mM       |
| 34802       | October 9  |         |              |     |        |              |      |              |               |              |            | 91 6     |
|             | October 10 |         |              |     | 200    | 82           | 16   | 4            | 1             | 21           | 4          |          |
|             |            |         |              |     | 230    | 31           | 7    | 0            | 0             | 2            | 0          |          |
|             | October 11 |         |              |     | 57     | 29           | 2    | 0            | 0             | 18           | 1          | 79 7     |
|             |            |         |              |     | 153    | 94           | 15   | 19           | 3             | 73           | 11         |          |
|             |            |         |              |     | 418    | 34           | 14   | 0            | 0             | 23           | 10         |          |
|             | October 14 |         |              |     | 78     | 50           | 4    | 6            | 0             | 28           | 2          |          |
|             | October 15 |         |              |     | 255    | 72           | 18   | 0            | 0             | 22           | 6          |          |
|             |            |         |              |     | 125    | 46           | 6    | 0            | 0             | 22           | 3          |          |
|             | October 19 |         |              |     | 200    | 79           | 16   | 9            | 2             | 38           | 8          | 82 8     |
|             | October 21 |         |              |     | 73     | 98           | 7    | 0            | 0             | 45           | 3          |          |
|             | October 22 |         |              |     | 136    | 89           | 12   | 0            | 0             | 24           | 3          |          |
|             |            |         |              |     | 160    | 123          | 20   | 0            | 0             | 50           | 8          |          |
|             | October 23 |         |              |     | 70     | 140          | 10   | 0            | 0             | 39           | 3          |          |
|             |            |         |              |     | 122    | 87           | 11   | 0            | 0             | 13           | 2          |          |
|             | Total      |         |              |     | 2,277  |              | 158  |              |               | 64           |            |          |
| 29267       | December 1 | 1,700   | 42           | 73  | 260    | 50           | 13   | 0            | 0             | 41           | 11         | 95 3     |
|             | December 2 | 2,200   | 51           | 111 | 230    | 62           | 14   | 12           | 3             | 73           | 17         |          |
|             | December 4 | 2,000   | 60           | 118 | 31     | 70           | 2    | 16           | 0             | 73           | 2          |          |
|             | December 5 | 2,300   | 68           | 156 | 186    | 96           | 18   | 8            | $\frac{1}{4}$ | 46           | 9          |          |
|             | Total      | 8,200   |              | 458 |        |              | 47   |              |               | 39           |            |          |
|             | December 6 |         |              |     |        |              |      |              |               |              |            | 96 2     |
| 56247       | January 13 | 1,170   | 38           | 32  |        |              | 3    |              |               |              |            | 92 5     |
|             | January 25 | 1,560   | 45           | 29  | 1,100+ | 45           | 41+  |              |               |              |            |          |
|             | January 26 | 980     | 34           | 34  | 1,400+ | 79           | 56+  |              |               |              |            |          |
|             | January 27 | 1,470   | 45           | 31  | 290+   | 55           | 19+  |              |               |              |            |          |
|             | Total      | 4,010   |              | 94  | 2,790+ |              | 116+ |              |               |              |            |          |

combination with endogenous carbonic acid while excreting the Cl neutralized by ammonia. In nephritis such adjustment is difficult, if not impossible. Therefore, to restore complete normal equilibrium, it may be necessary to administer bicarbonate as well as chloride at times.

de Wesselow (8) has suggested that vomiting is itself an adaptive

TABLE 5—Continued

| Case number | Date       | Urne       |              |     | Vomit  |     |              |    |              |    |              |      | Serum Cl |
|-------------|------------|------------|--------------|-----|--------|-----|--------------|----|--------------|----|--------------|------|----------|
|             |            | Vol ume    |              | Cl  | Volume |     | Cl           |    | Free acid    |    | Total acid   |      |          |
|             |            | cc         | mM per liter |     | mM     | cc  | mM per liter | mM | mM per liter | mM | mM per liter | mM   |          |
| 34802       | October 9  |            |              |     |        |     |              |    |              |    |              |      | 91 6     |
|             | October 10 |            |              |     | 200    | 82  | 16           | 4  | 1            | 21 | 4            |      |          |
|             |            |            |              |     | 230    | 31  | 7            | 0  | 0            | 2  | 0            |      |          |
|             | October 11 |            |              |     | 57     | 29  | 2            | 0  | 0            | 18 | 1            |      |          |
|             |            |            |              |     | 153    | 94  | 15           | 19 | 3            | 73 | 11           |      |          |
|             |            |            |              |     | 418    | 34  | 14           | 0  | 0            | 23 | 10           |      |          |
|             | October 14 |            |              |     | 78     | 50  | 4            | 6  | 0            | 28 | 2            | 79 7 |          |
|             | October 15 |            |              |     | 255    | 72  | 18           | 0  | 0            | 22 | 6            |      |          |
|             |            |            |              |     | 125    | 46  | 6            | 0  | 0            | 22 | 3            |      |          |
|             | October 19 |            |              |     | 200    | 79  | 16           | 9  | 2            | 38 | 8            |      |          |
|             | October 21 |            |              |     | 73     | 98  | 7            | 0  | 0            | 45 | 3            |      |          |
|             | October 22 |            |              |     | 136    | 89  | 12           | 0  | 0            | 24 | 3            |      |          |
|             |            |            |              |     | 160    | 123 | 20           | 0  | 0            | 50 | 8            | 82 8 |          |
|             | October 23 |            |              |     | 70     | 140 | 10           | 0  | 0            | 39 | 3            |      |          |
|             |            |            |              | 122 | 87     | 11  | 0            | 0  | 13           | 2  |              |      |          |
|             | Total      |            |              |     | 2,277  |     | 158          |    |              | 64 |              |      |          |
| 29267       | December 1 | 1,700      | 42           | 73  | 260    | 50  | 13           | 0  | 0            | 41 | 11           | 95 3 |          |
|             | December 2 | 2,200      | 51           | 111 | 230    | 62  | 14           | 12 | 3            | 73 | 17           |      |          |
|             | December 4 | 2,000      | 60           | 118 | 31     | 70  | 2            | 16 | 0            | 73 | 2            |      |          |
|             | December 5 | 2,300      | 68           | 156 | 186    | 96  | 18           | 8  | 1            | 46 | 9            |      |          |
|             | Total      | 8,200      |              | 458 |        |     | 47           |    | 4            |    | 39           |      |          |
|             | December 6 |            |              |     |        |     |              |    |              |    |              | 96 2 |          |
|             | 56247      | January 13 | 1,170        | 38  | 32     |     |              | 3  |              |    |              |      |          |
| January 25  |            | 1,560      | 45           | 29  | 1,100+ | 45  | 41+          |    |              |    |              | 92 5 |          |
| January 26  |            | 980        | 34           | 34  | 1,400+ | 79  | 56+          |    |              |    |              |      |          |
| January 27  |            | 1,470      | 45           | 31  | 290+   | 55  | 19+          |    |              |    |              |      |          |
| Total       |            | 4,010      |              | 94  | 2,790+ |     | 116+         |    |              |    |              |      |          |

combination with endogenous carbonic acid while excreting the Cl neutralized by ammonia. In nephritis such adjustment is difficult, if not impossible. Therefore, to restore complete normal equilibrium, it may be necessary to administer bicarbonate as well as chloride at times.

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be permeable to anions, peculiarities of distribution appear that suggest that such permeability is relative. It is, apparently, conditioned by (a) certain acid patterns that are characteristic of individual tissues and (b) the need for readjustments in response to local endogenous acid production.

Such considerations alone would make the estimation of the chloride content of the body, or even its changes, from corresponding serum concentrations exceedingly hazardous. The data that have been presented dealing with salt balances indicate that, in general, increases in blood salt concentration, other things being equal, are associated with retention of salt. Attempts to relate the two quantitatively have not been eminently successful. Besides the incalculable distribution of Cl in body fluids and tissues, the proportions of these fluids and tissues themselves are constantly changing to increase the difficulty. In certain studies that will be presented later attempts have been made to estimate gains or losses in tissue by means of the nitrogen balance and, employing these for the correction of weight changes, to determine by difference alterations of the water content of the body. Similar methods applied to some of the cases of this series tend to show that the body water content in advanced nephritis is quite variable and that fluctuations in water content are attended by similar changes in salt balance.

Although it is quite evident that blood water and tissue water are not always closely related, in the majority of instances anhydremia is attended by hemo-concentration. Striking exceptions may be pointed out, usually in the presence of edema, when the blood may be inspissated while the tissues contain an excess of fluid. Examples of this may be found in a diabetic case previously reported by the authors (9), and in one case of this series. With the exception of such cases, however, in which hydrostatic factors may have played the chief part, the water content of the blood seems to reflect changes in the hydration of the body as a whole.

Attention has already been called to the variability of serum proteins in this series of cases and to the probability that these variations are partly due to changes in blood water. Simultaneous determinations of serum volume by the dye method of Keith, Rowntree and Geraghty (10), in case no. 56247 have shown that this is the case. The results

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## CONCLUSIONS

Hypochloremia and deficiency of base in the serum in advanced nephritis seem to be the results of:

1 A tendency for both base and chloride to be excreted in the urine when serum Cl has fallen below the level which, in the normal individual determines achloruria

2 Vomiting, which attains its effect less by producing direct chloride loss than by interfering with salt intake

a The vomitus in uremia contains little free hydrochloric acid. A considerable amount of the Cl in such vomitus exists in the form of BCl

b Although the concentration of Cl in vomitus remains high even in the face of advanced hypochloremia the total Cl loss by emesis is usually small compared with that in the urine

3 Considerable quantities of Cl may be lost in the feces in certain cases even if there is no diarrhea

There is no necessity of postulating any peculiar redistribution of chlorides in the body to explain the hypochloremia

The distribution of Cl is discussed as are the relations of changes in body water and salt content. It is pointed out that hypochloremia and low serum base are usually attended by anhydremia and general dehydration

The therapeutic implications of these findings are discussed

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- 2 Vomiting, which attains its effect less by producing direct chloride loss than by interfering with salt intake

- a The vomitus in uremia contains little free hydrochloric acid. A considerable amount of the Cl in such vomitus exists in the form of BCl

- b Although the concentration of Cl in vomitus remains high even in the face of advanced hypochloremia the total Cl loss by emesis is usually small compared with that in the urine

- 3 Considerable quantities of Cl may be lost in the feces in certain cases even if there is no diarrhea

There is no necessity of postulating any peculiar redistribution of chlorides in the body to explain the hypochloremia

The distribution of Cl is discussed as are the relations of changes in body water and salt content. It is pointed out that hypochloremia and low serum base are usually attended by anhydremia and general dehydration

The therapeutic implications of these findings are discussed

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few leucocytes or red blood cells. A year after discharge albuminuria persisted, but edema had not returned as long as he continued treatment. His blood pressure was 164/88 on one occasion, at other times normal. In 1924 he had become infected with syphilis and his Wassermann was found to be strongly positive.

*Case no 35628* (Protocol given at length in a previous paper (3)), a Polish male, aged 43, four months before admission, after tonsillitis, developed generalized subcutaneous edema, double hydrothorax and ascites. His blood pressure was normal. The urine contained much albumin, many casts, moderate numbers of leucocytes and variable numbers of red blood cells. Early in his course in the hospital he had two attacks of sore throat with fever. His edema did not subside until after tonsillectomy, March 17th.

*Case no 34854* (Protocol of first admission given at length in a previous paper (3)), a Polish male, aged 29, was admitted with generalized subcutaneous edema, double hydrothorax, ascites and splenic enlargement, which had first appeared two years earlier after an attack of polyarthritis and had been aggravated by frequent sore throats which had continued even after tonsillectomy. His blood pressure was 155/95 on admission, but soon fell to normal. His urine contained much albumin, many casts and leucocytes and variable numbers of red blood cells (sometimes gross blood). His course was marked by attacks of sore throat associated with fever and exaggeration of the hematuria. He was discharged in August, but returned the next June, after a prolonged stay in another hospital, temporarily free from edema, but sick and emaciated. After July 10th, symptoms and signs suggesting embolic phenomena appeared with increasing frequency. September 19th and October 8th he had typical apoplectic seizures and died shortly after the second.

Autopsy revealed a massive cerebral hemorrhage, evidences of old and recent infarcts in several organs, a single, small fresh vegetation on the mitral valve, and large, swollen, kidneys that presented evidences of focal embolic lesions, diffuse glomerular nephritis and tubular degenerative changes.

*Case 56883* An American male, aged 21, was admitted because of a profuse albuminuria that had developed after a severe attack of "grippe" five years earlier. His blood pressure was normal. The urine contained much albumin and moderate numbers of casts and leucocytes.

*Case no 50265* A Swiss male, aged 36, with tuberculosis of the upper lobe of the left lung and a chronic discharging right ear, developed edema of the lower extremities six months earlier. His blood pressure was normal. The urine contained large amounts of albumin and many casts, but no red blood cells nor leucocytes.

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Bacteriological studies of the urine, blood and throat or other possible foci of infection were made in most cases. Cultures of the urine proved sterile in cases 29122, 50265, 56883, 56577, 61090, 62246, 61711 and 34753. The urines of 50256, 56577 and 34753 were also repeatedly examined for tubercle bacilli but none were found, cultures and guinea pig inoculations were also negative. Blood cultures from 34854 were repeatedly negative, although the urine cultures on several occasions yielded non-hemolytic streptococci. Urine cultures from 35628, on two occasions recovered a Gram-negative, non-motile bacillus which produced no acid on most sugars and was not agglutinated by the patient's serum. Cultures from the abscess of 56577 yielded staphylococci. Throat cultures from 61090 revealed chiefly non-hemolytic, but some hemolytic streptococci. In the case of 61711, hemolytic streptococci were obtained repeatedly from the throat during the acute infections, the same organisms were later recovered from the mastoid, and finally from the blood and the peritoneal cavity.

Besides the examinations of the blood which are presented in the table, studies of nitrogen and chloride in food and urine were made on cases 35628, 34854 and 50265. Stools and vomitus of cases 61090, 62246, 61711 and 34753 were also examined for the same constituents. The notes on chloride balance in the table are derived from these data, which will be presented in more detail in another paper.

As a matter of routine all patients, as long as edema was evident, received diets which contained not more than 2 grams of Cl (as NaCl) daily. Limitation of fluid was purposely practised only while edema was extreme. Fluid intakes were, however, seldom large because, deprived of salt, patients lost their desire for water. When edema could no longer be detected increasing measured amounts of salt were given, these were discontinued if evident retention of fluid ensued. If rest, diet and salt regulation were not followed by diuresis, ammonium chloride, urea and sometimes other diuretic drugs were given.

#### ANALYSIS OF RESULTS

The results of electrolyte studies with weights of patients and notes on edema and salt balance are presented in table 1.

No attempt will be made in this discussion to differentiate the nephroses from the glomerular nephritides. In the authors' opinion such a differentiation on a functional basis is impossible and on a clinical basis extremely difficult. Only a classification on etiological grounds can be of great value. At certain stages of the disease 29122, 31190, 50265, 56883, 56577, 61090, 62246, 61711 and 34753 presented the characteristics of nephrosis. Of these 34753 proved to have a true amyloid nephrosis. Case nos 50265 and 56577, with pulmonary tuberculosis and chronic osteomyelitis respectively, may well have the

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Bacteriological studies of the urine, blood and throat or other possible foci of infection were made in most cases. Cultures of the urine proved sterile in cases 29122, 50265, 56883, 56577, 61090, 62246, 61711 and 34753. The urines of 50256, 56577 and 34753 were also repeatedly examined for tubercle bacilli but none were found, cultures and guinea pig inoculations were also negative. Blood cultures from 34854 were repeatedly negative, although the urine cultures on several occasions yielded non-hemolytic streptococci. Urine cultures from 35628, on two occasions recovered a Gram-negative, non-motile bacillus which produced no action on most sugars and was not agglutinated by the patient's serum. Cultures from the abscess of 56577 yielded staphylococci. Throat cultures from 61090 revealed chiefly non-hemolytic, but some hemolytic streptococci. In the case of hemolytic streptococci were obtained repeatedly from the throat during infections, the same organisms were later recovered from the mastoid, from the blood and the peritoneal cavity.

Besides the examinations of the blood which are presented in the report, analyses of nitrogen and chloride in food and urine were made on cases 34854, 50265. Stools and vomitus of cases 61090, 62246, 61711 and 34753 were also examined for the same constituents. The notes on chloride balance are derived from these data, which will be presented in another paper.

As a matter of routine all patients, as long as edema was present, were given a diet which contained not more than 2 grams of Cl (as NaCl). This was purposely practised only while edema was excessive, but was not continued, however, seldom large because, deprived of salt water. When edema could no longer be detected, the diet was changed. If analyses of salt were given, these were discontinued if edema had subsided. Rest, diet and salt regulation were not followed in cases 34854, 50265, 56883, 56577, 61090, 62246, 61711 and 34753. Urea and sometimes other diuretic drugs were given in cases 34854, 50265, 56883, 56577, 61090, 62246, 61711 and 34753.

#### ANALYSIS OF CASES

The results of electrolyte studies on edema and salt balance are presented in the following tables.

No attempt will be made in this paper to differentiate between the various types of renal disease on a functional basis, although this is extremely difficult. The results of the studies can be of great value in the diagnosis of cases 50265, 56883, 56577, 61090, 62246, 61711 and 34753, the characteristics of which are typical of amyloid nephrosis, tuberculous nephritis and chronic glomerular nephritis.

TABLE 1—Continued

| Case number | Date               | Weight<br>kgm | Serum total protein* |      | Albumin<br>m eq | Globulin<br>m eq | HCO <sub>3</sub> |       | Cl     |      | Inorganic P |      | Acid 1 + 2 + 3 + 4 |       | Base |      | Undetermined acid 6-5 |       | Blood non protein nitro-<br>gen<br>mgm<br>per 100<br>cc | Phenolsulphonethalein<br>test<br>per<br>cent | Edema | Cl balance | Diet NaCl† | Treatment†         |
|-------------|--------------------|---------------|----------------------|------|-----------------|------------------|------------------|-------|--------|------|-------------|------|--------------------|-------|------|------|-----------------------|-------|---|--|-------|------------|------------|--------------------|
|             |                    |               | m eq                 | m eq |                 |                  | m eq             | m eq  | m eq   | m eq | m eq        | m eq | m eq               | m eq  | m eq | m eq | m eq                  | m eq  |   |  |       |            |            |                    |
| 56577       | 1928<br>March 23   |               | 13.5                 | 7.8  | 5.6             |                  | 26.3             | 103.6 | 2.3    |      |             |      | 145.7              | 150.2 |      |      | 4.5                   | 27    |   |  | ±     |            |            |                    |
|             | 1926<br>October 21 | 66.5          | 7.4                  |      |                 |                  | 33.0             | 100.8 | 3.0    |      |             |      | 144.2              | 142.9 |      |      | -1.3                  | 31    |   |  | +     |            | 0          |                    |
| 34753       | October 29         | 66.5          | 7.9                  |      |                 |                  | 30.2             | 101.2 | 3.0    |      |             |      | 142.3              | 141.1 |      |      | -1.2                  | 33    |   |  | +     |            | 0          |                    |
|             | November 6         | 65.2          | 7.1                  |      |                 |                  | 29.6             | 101.0 | 2.7    |      |             |      | 140.4              | 144.8 |      |      | 4.4                   | 35    |   | 48   | +     |            | 0          |                    |
|             | November 16        | 66.1          | 7.4                  |      |                 |                  | 30.5             | 105.5 | 8.3**  |      |             |      | 151.7**            | 150.9 |      |      | -0.8**                | 25    |   |  | +     |            | 0          |                    |
|             | December 2         | 65.2          | 9.2                  |      |                 |                  | 31.1             | 99.5  | 2.3    |      |             |      | 142.1              | 141.3 |      |      | -0.8                  | 30    |   |  | +     |            | 0          |                    |
|             | December 9         | 66.8          | 8.5                  |      |                 |                  | 30.9             | 104.8 | 3.1    |      |             |      | 147.3              | 155.9 |      |      | 8.6                   | 27    |   | 50   | +     |            | 0          |                    |
|             | December 18        | 64.0          | 8.5                  |      |                 |                  | 30.6             | 102.4 | 10.0** |      |             |      | 151.5**            | 146.0 |      |      | -5.5**                | 10s†† |   |  | +     |            | 0          |                    |
|             | December 23        | 63.4          | 8.6                  |      |                 |                  | 25.2             | 109.7 | 2.8    |      |             |      | 146.3              | 144.9 |      |      | -1.4                  | 23    |   |  | +     |            | 0          | NH <sub>4</sub> Cl |
|             | 1927<br>January 7  | 68.0          | 10.4                 |      |                 |                  | 30.2             | 103.4 | 2.8    |      |             |      | 146.8              | 144.9 |      |      | -1.9                  | 23    |   |  | +     |            | 0          |                    |
|             | February 16        | 57.8          | 8.5                  |      |                 |                  | 28.9             | 104.4 | 2.2    |      |             |      | 144.0              | 142.0 |      |      | -2.0                  | 32    |   |  | +     |            |            |                    |
|             | April 8            | 71.3          | 9.0                  |      |                 |                  | 30.0             | 105.2 | 2.5    |      |             |      | 146.7              | 149.6 |      |      | 2.9                   | 25    |   |  | +     |            |            |                    |
|             | July 1             |               | 8.2                  |      |                 | 6.0              | 2.3              | 104.4 | 2.2    |      |             |      | 144.2              | 151.9 |      |      | 7.7                   | 29    |   |  | +     |            |            |                    |
|             | July 22            | 70.6          | 7.8                  |      |                 | 4.2              | 3.5              | 105.8 |        |      |             |      |                    |       |      |      | 27                    |       |   |  | +     |            |            |                    |
|             | 1928<br>January 13 |               | 7.2                  |      |                 | 3.4              | 3.8              | 107.8 | 2.7    |      |             |      | 140.8              | 155.8 |      |      | 15.0                  | 56    |   |  | +     |            | +          |                    |
|             | February 4††       | 73.0          | 7.5                  |      |                 | 3.7              | 3.8              | 103.4 | 4.4    |      |             |      | 131.6              | 142.3 |      |      | 10.7                  | 85    |   |  | +     |            | +          |                    |
|             | February 8††       |               | 8.8                  |      |                 | 4.5              | 4.3              | 96.4  | 6.9    |      |             |      | 126.8              | 141.2 |      |      | 14.4                  | 155   |   |  | 0     |            | +          |                    |
|             | February 10††      |               | 8.6                  |      |                 | 5.6              | 3.1              | 89.0  | 11.1   |      |             |      |                    |       |      |      | 238                   |       |   |  | 0     |            | +          |                    |
|             | February 12††      |               | 5.6                  |      |                 | 3.7              | 1.9              | 88.0  | 12.2   |      |             |      |                    | 152.8 |      |      | 301                   |       |   |  |       |            | +          |                    |

Pentonitis

Post-mortem pleu-  
ral fluid

TABLE 1—Continued

| Case number | Date               | Weight<br>kgm | Serum total protein* |     | Albumin<br>gm | Globulin<br>gm | HCO <sub>3</sub><br>m eq | Cl<br>m eq | Inorganic P<br>mg | Acid 1 + 2 + 3 + 4<br>m eq | Base<br>m eq | Undetermined acid 6-5<br>m eq | Blood non protein nitro-<br>gen<br>mgm per 100 cc | Phenolsulphonethalein<br>test | Edema | Cl balance | Diet NaCl | Treatment†                     |
|-------------|--------------------|---------------|----------------------|-----|---------------|----------------|--------------------------|------------|-------------------|----------------------------|--------------|-------------------------------|---|-------------------------------|-------|------------|-----------|--------------------------------|
|             |                    |               | 1                    | 2   |               |                |                          |            |                   |                            |              |                               |   |                               |       |            |           |                                |
| 56577       | 1928<br>March 23   |               | 13.5                 | 7.8 | 5.6           |                | 26.3                     | 103.6      | 2.3               | 145.7                      | 150.2        | 4.5                           | 27  |                               | ±     |            |           |                                |
| 34753       | 1926<br>October 21 | 66.5          | 7.4                  |     |               |                | 33.0                     | 100.8      | 3.0               | 144.2                      | 142.9        | -1.3                          | 31  |                               | +     |            | 0         |                                |
|             | October 29         | 66.5          | 7.9                  |     |               |                | 30.2                     | 101.2      | 3.0               | 142.3                      | 141.1        | -1.2                          | 33  |                               | +     |            | 0         |                                |
|             | November 6         | 65.2          | 7.1                  |     |               |                | 29.6                     | 101.0      | 2.7               | 140.4                      | 144.8        | 4.4                           | 35  | 48                            | +     |            | 0         |                                |
|             | November 16        | 66.1          | 7.4                  |     |               |                | 30.5                     | 105.5      | 8.3**             | 151.7**                    | 150.9        | -0.8**                        | 25  |                               | +     |            | 0         |                                |
|             | December 2         | 65.2          | 9.2                  |     |               |                | 31.1                     | 99.5       | 2.3               | 142.1                      | 141.3        | -0.8                          | 30  |                               | +     |            | 0         |                                |
|             | December 9         | 66.8          | 8.5                  |     |               |                | 30.9                     | 104.8      | 3.1               | 147.3                      | 155.9        | 8.6                           | 27  | 50                            | +     |            | 0         |                                |
|             | December 18        | 64.0          | 8.5                  |     |               |                | 30.6                     | 102.4      | 10.0**            | 151.5**                    | 146.0        | -5.5**                        | 10s††   |                               | +     |            | 0         |                                |
|             | December 23        | 63.4          | 8.6                  |     |               |                | 25.2                     | 109.7      | 2.8               | 146.3                      | 144.9        | -1.4                          | 23  |                               | +     |            | 0         | NH <sub>4</sub> Cl             |
|             | 1927<br>January 7  | 68.0          | 10.4                 |     |               |                | 30.2                     | 103.4      | 2.8               | 146.8                      | 144.9        | -1.9                          | 23  |                               | +     |            | 0         |                                |
|             | February 16        | 57.8          | 8.5                  |     |               |                | 28.9                     | 104.4      | 2.2               | 144.0                      | 142.0        | -2.0                          | 32  |                               | +     |            |           |                                |
|             | April 8            | 71.3          | 9.0                  |     |               |                | 30.0                     | 105.2      | 2.5               | 146.7                      | 149.6        | 2.9                           | 25  |                               | +     |            |           |                                |
|             | July 1             |               | 8.2                  | 6.0 | 2.3           |                | 29.4                     | 104.4      | 2.2               | 144.2                      | 151.9        | 7.7                           | 29  |                               | +     |            |           |                                |
|             | July 22            | 70.6          | 7.8                  | 4.2 | 3.5           |                | 28.1                     | 105.8      |                   |                            |              |                               | 27  |                               | +     |            |           |                                |
|             | 1928<br>January 13 |               | 7.2                  | 3.4 | 3.8           |                | 23.1                     | 107.8      | 2.7               | 140.8                      | 155.8        | 15.0                          | 56  |                               | +     |            | +         |                                |
|             | February 4††       | 73.0          | 7.5                  | 3.7 | 3.8           |                | 16.3                     | 103.4      | 4.4               | 131.6                      | 142.3        | 10.7                          | 85  |                               | +     |            | +         |                                |
|             | February 8††       |               | 8.8                  | 4.5 | 4.3           |                | 14.7                     | 96.4       | 6.9               | 126.8                      | 141.2        | 14.4                          | 155   |                               | 0     |            | +         |                                |
|             | February 10††      |               | 8.6                  | 5.6 | 3.1           |                |                          | 89.0       | 11.1              |                            |              |                               | 238   |                               | 0     |            | +         |                                |
|             | February 12††      |               | 5.6                  | 3.7 | 1.9           |                |                          | 88.0       | 12.2              |                            | 152.8        |                               | 301   |                               | 0     |            | +         | Post-mortem pleu-<br>ral fluid |

tionated estimation of the base combined with it is too large. In the same studies, then, the estimated value for "undetermined acid" is correspondingly too small. This offers an adequate explanation for most of the negative (base < total determined acid) values recorded. Some of these (34854, December 6 and 34753, December 18), however, are so large that they can hardly be explained on this score. Furthermore, similar negative values were found in two instances when proteins were fractionated, 61090, September 21 and 62246, November 15. (There is some reason to doubt the accuracy of the determinations on 31190, June 4 and 62246, February 7.) It is hard to believe that the sum of acid equivalents in blood serum can ever exceed that of base, it is almost as hard to believe that the estimations of combining equivalents of acids other than protein can be greatly in error. It is also worthy of note that similar negative values have not been found in a large number of observations of normal human subjects, and have been encountered extremely rarely in patients with other pathological conditions.

On the whole organic acid concentration is seldom high and usually quite low. High values seem to appear at certain stages of the disease in individual cases only, and may well be due not to the renal disease itself, but to some concomitant symptoms or conditions such as intercurrent infections or vomiting.

*Inorganic phosphate*, with few exceptions, lay within the limits of normal variation. It usually fell slightly as edema disappeared and patients improved. Minor fluctuations can be observed following certain therapeutic measures, especially ammonium chloride. The latter will be discussed elsewhere. Occasionally decidedly high figures were obtained without any evident reason, notably in cases 34753, November 16 and December 18, and 61090, October 25 and 31. (The last two values in 34753 must be laid to the effects of peritonitis.) So suddenly and unexpectedly do these high levels appear and disappear that one is inclined to ascribe them to technical errors. Duplicates checked well and normal values were obtained from other patients on the same days. The sera were separated so expeditiously and with such care that there is no reason to believe that phosphorus escaped from cells to serum. In extensive studies of normal and diabetic sera no such high values were ever found. In this series they

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*Bicarbonate* Reduction of bicarbonate, when it occurs, does not seem to be due to accumulation in the blood of abnormal acids. Organic acid and phosphate are seldom elevated. Bicarbonate deficit (acidosis) is usually associated with hyperchloremia, low base or both. Because protein is low, bicarbonate is forced to yield less than it otherwise would to these factors and serious bicarbonate deficits are seldom observed except after ammonium chloride. When Cl remains normal as in 34753 and 62246, bicarbonate is often high in spite of base deficiency, by virtue of the small base combining powers of the diminished protein.

*Base* The outstanding feature of the total base values is their variability. This is illustrated in figure 1. Of the 59 base determinations 35 lie either above or below the normal limits. The distribution of these abnormal values is illuminating. 29, or almost half of the total number of observations are low, while only 6 are high. Certainly, in this series of cases, base deficiency is far more common than base excess. The proportions of water to solids in several instances was directly determined. The weight of solids, as was expected, tended to parallel the protein concentration<sup>1</sup> and was therefore, low. This would seem to establish the fact that the total concentration of electrolytes per unit of water in the sera of these subjects was low, a condition which should cause the osmotic pressure to fall below the usual level (hypotonicity). Often enough this condition may have been produced or favored by the treatment, restriction of salt without purposeful restriction of fluids. It was, however, found (in case 34753 for example) before treatment.

The level of base bore no direct relation to that of any other serum component studied, nor was it associated with the concentration of non-protein nitrogen in the blood.

#### DISCUSSION

Only one abnormal feature is characteristically and consistently encountered in the electrolyte picture in the sera of patients with the hypopigmentous nephritides: this is reduction of the concentration of protein, and especially the albumin fraction. Furthermore, this is

<sup>1</sup> Presumably because of their large lipid content, sera from these patients contained a larger quantity of solids in proportion to protein than was found in the sera of other patients.

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the only change that can be related with any consistency to the occurrence of or tendency to edema. Figure 2 shows that edema was almost invariably found when the total serum proteins were less than 4 per cent and never occurred when they exceeded 5 per cent. Linder, Lundsgaard and Van Slyke (9) found a similar relation between tendency to edema and protein concentration. This lends considerable support to the theory of Govaerts (10) and Schade and Claussen (11). They believe that protein deficiency, by reducing the colloid osmotic pressure of the serum, diminishes the force which ordinarily resists the tendency of hydrostatic pressure (blood pressure) to force fluid through the capillary walls into the tissues. In the edematous nephritides the colloid osmotic pressure is reduced even more than the total serum protein concentration would indicate, because the osmotic pressure of a gram of albumin is, as Govaerts (12) has shown, much greater than that of a gram of globulin.

Alterations of organic acid and phosphorus are rare and must play an unimportant part in the pathogenesis of edema and other symptoms.

Bicarbonate also appears to occupy a rather insignificant, if helpful position. Its behavior seems to illustrate beautifully what Gamble (13) has called its "mendicant position." It effaces itself as far as possible when there is too little base to completely satisfy inflated  $\text{Cl}$ , thankfully accepts what base the weakened proteins can no longer hold. It is hard to believe that it is acting more than a helpful secondary rôle, fitting in where it may prove useful.

Base has been found to be quite variable, sometimes above and sometimes below the normal limits. In this series it was low in about one-half the determinations, high in only about one-tenth. With the reasonable assumption that base is distributed in approximately uniform concentration throughout the fluids of the body, the frequent occurrence of base deficit is a cogent argument against the generally accepted theory that water accumulations in nephritic edema are entirely secondary to retention of sodium. Reductions of serum base are, perhaps, more frequent in the studies here reported because a more purposeful effort was made to restrict salt in the diet than to limit the fluid intake. However, low base concentrations were found in the sera of some patients before treatment was instituted.

Serum base excess was observed especially during the earlier part of the hospital course of patients 35628 and 34854. At these times both

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the base changes here reported. For the latter, alterations of sodium concentration must be chiefly responsible. In this case repositories in which it may be retained are presumably extracellular,—i.e., the edema transudates themselves. Examinations of such transudates by others (15) and in case 61090 have invariably failed to reveal base concentrations higher in relation to those of the serum than would be anticipated on the basis of current theories of osmotic equilibrium. Cl distribution is not so uniform (16), in two instances in the present investigation (61711 and 61090) the chloride concentration of transudates proved far higher than that of serum.

In about one-third of the determinations the concentration of Cl was distinctly above the normal limits of variation, while hypochlor-emia was never observed. This again is hard to explain on the theory that it is the basic ion  $\text{Na}^+$  and not the acid  $\text{Cl}^-$  which is chiefly retained by patients with nephritic edema. The chloride excess can not be looked upon merely as a compensatory reaction against protein deficit because it is sometimes so large (35628, January 13, 34854, October 16, 23, 28, November 6) that, with base normal or high, it makes up for the protein deficit and forces a recession of bicarbonate as well. This would indicate that in the hydropigenous nephritides the  $\text{Cl}^-$  ion is usually excreted with the greatest difficulty.<sup>2</sup> Nor is there any direct or indirect evidence of importance to prove that this is not the case. Hyperchloremia has been found frequently by other observers (16, 17), high base rarely (14, 16, 17).

Changes in the concentration of the inorganic electrolytes can not be directly connected with the presence or absence or degree of edema. This is clearly shown in figures 1 and 2. Extremely distorted electrolyte patterns are less often noted in the absence of edema, but the number of blood studies on non-edematous patients are, for obvious reasons, too few to permit valid comparison. Distinctly abnormal electrolyte pictures involving disturbances of base, Cl and  $\text{HCO}_3$  were certainly encountered when no edema could be detected. Due consideration must, of course, be given to the fact that absence of edema was produced and maintained in most instances only by contin-

<sup>2</sup> The authors do not mean to imply that the faulty excretion is necessarily due to abnormalities in the renal mechanism.

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nous tendency was at its worst, the production of extreme hyperchloremia and consequent acidosis was entirely ineffectual as a diuretic measure (34854, November 13 to 18, 34753, December 18 to 23, 61090, July 6 to 14) Salt poor diets in which both base and Cl were presumably low were more often followed by a fall of serum base than reduction of serum chloride All these results indicate that the Cl ion is excreted with extreme difficulty

Gamble (17) has suggested that the hyperchloremia is a reaction which promotes diuresis in these cases With this point of view the authors agree, but not with the apparent implication that it is a favorable adaptive reaction It is merely the direct result of failure to excrete Cl When this failure produces a sufficiently unbalanced electrolyte pattern diuresis results Diuresis may be induced by exaggerating the imbalance by giving ammonia chloride

By the same reasoning one would expect bicarbonate to favor retention of water If there is a specific excess of Cl or any other acid ion in the blood the administration of bicarbonate is equivalent to giving so much base The bicarbonate ion is excreted by the lungs, leaving the base to combine with the Cl This is, of course, a step towards the restoration of a normal electrolyte picture and must, therefore, remove the stress which was forcing diuresis

Transferring emphasis from sodium to chloride and water alters current therapy but little Restriction of salt remains the most practical routine procedure Diets poor in Cl are also poor in base Without salt the desire to take fluids diminishes, therefore the restriction of salt results in fluid limitation without distressing the patient

#### SUMMARY

- 1 The concentration of base and the most important acids (protein, bicarbonate, chloride and inorganic phosphate) in the serum, together with the nitrogen and chloride metabolism of patients with nephrosis and nephrotic types of chronic glomerular nephritis have been determined

- 2 Neither the level of proteins in the serum nor the electrolyte pattern permits differentiation between nephrosis and the nephrotic type of chronic glomerular nephritis

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provement clinically on the other, it seemed desirable to study further the creatine-creatinine metabolism in this disease as influenced by the administration of iodine. Furthermore, the intimate association of creatine and creatinine with muscle function and the important and striking symptom of muscular weakness in this disease add interest to the observation we desire to report.

#### EXPERIMENTAL

Cases of exophthalmic goiter were studied in a specially organized metabolism ward in order to insure proper dietary control and accurate collection of urinary specimens. The diets employed were creatine-free with a caloric value equivalent to 100 per cent above the actually determined basal requirement. The protein was fixed between 1 and  $1\frac{1}{2}$  grams per kilogram, the carbohydrate and fat distributed according to the individual preferences of the subject. Invariably the carbohydrates were more freely taken than the fats. Such a diet in our experience has established nitrogen equilibrium or a positive nitrogen balance within three or four days. After a period of three days to a week iodine was administered as Lugol's solution in 1 to 3 cc amounts daily, in practically all instances as part of the preparation for partial thyroidectomy. Creatine and creatinine were determined by the usual Folin method. All specimens of urine were examined for ketone bodies before the determinations were made. At the outset during the winter 1925-1926 uric acid and nitrogen balances were determined. Later these observations were discontinued for reasons given later.

Eight of the cases reported in this paper were studied by D. A. C. in the Lane and Stanford University Hospital in San Francisco during the winter of 1927 and 1928. Some of these patients received iodine in the form of sodium iodide either alone or in association with Lugol's solution.

#### RESULTS

For convenience in discussion the 43 cases studied are divided into two groups and arranged in order of the elevation of the basal metabolic rate in tables 1 and 2. The first group, table 1, includes the cases quite generally recognized as true exophthalmic goiter, and the second group in table 2 the subjects, as a rule older, without exophthalmos.

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TABLE I  
*Exophiala* goser Group I  
 Cases arranged in order of the initial basal metabolic rate

| Case number | Hospital record number | Sex | Age | Weight<br>kgm | Basal metabolic rate above normal |                  | Creatine          |                  | Creatinine        |                  | Creatinine coefficient | Days before effect | Remarks   |
|-------------|------------------------|-----|-----|---------------|-----------------------------------|------------------|-------------------|------------------|-------------------|------------------|------------------------|--------------------|---|
|             |                        |     |     |               | Before<br>Lugol's                 | After<br>Lugol's | Before<br>Lugol's | After<br>Lugol's | Before<br>Lugol's | After<br>Lugol's |                        |                    |   |
| 1           | 67755                  | F   | 31  | 62            | 90                                | 48               | 0 58              | 0 00             | 0 60              | 0 53             | 10                     | 7                  |   |
| 2*          | 169712                 | M   | 36  | 55            | 82                                | 26               | 1 51              | 0 09             | 1 15              | 0 91             | 21                     | 3                  |   |
| 3*          | 141738                 | M   | 35  | 49            | 79                                | 32               | 1 08              | 0 05             | 1 03              | 0 75             | 21                     | 7                  |   |
| 4           | 71191                  | F   | 17  | 46            | 79                                | 62               | 0 25              | 0 00             | 0 40              | 0 45             | 9                      | 8                  |   |
| 5           | 70682                  | F   | 22  | 57            | 71                                | 15               | 0 65              | 0 03             | 0 60              | 0 60             | 11                     | 6                  |   |
| 6           | 67955                  | F   | 38  | 53            | 65                                | 15               | 0 43              | 0 00             | 0 80              | 0 90             | 15                     | 4                  |   |
| 7           | 67911                  | F   | 31  | 59            | 65                                | 15               | 0 50              | 0 00             | 0 60              | 0 70             | 10                     | 3                  |   |
| 8*          | 172491                 | F   | 21  | 57            | 62                                | 30               | 0 40              | 0 10             | 0 80              | 0 80             | 14                     | 7                  |   |
| 9           | 65916                  | M   | 37  | 50            | 62                                | 23               | 0 20              | 0 00             | 0 70              | 0 70             | 14                     | 3                  | Colored   |
| 10          | 67444                  | F   | 21  | 63            | 60                                | 15               | 0 70              | 0 05             | 0 90              | 0 80             | 14                     | 3                  |   |
| 11*         | 171003                 | F   | 26  | 52            | 58                                | 16               | 1 00              | 0 30             | 0 95              | 0 50             | 18                     | 5                  |   |
| 12          | 70353                  | F   | 32  | 59            | 58                                | 23               | 0 59              | 0 05             | 0 90              | 0 80             | 15                     | 6                  |   |
| 13          | 71150                  | M   | 42  | 62            | 56                                | 29               | 0 40              | 0 00             | 0 60              | 0 40             | 10                     | 3                  | Colored   |
| 14          | 68592                  | F   | 26  | 36            | 55                                | 30               | 0 55              | 0 03             | 0 60              | 0 60             | 17                     | 3                  | Colored   |
| 15          | 65566                  | F   | 27  | 43            | 55                                | 17               | 0 50              | 0 02             | 0 70              | 0 70             | 16                     | 3                  | The creatine excretion was quite irregular in this case until after iodine was started  |
| 16          | 68083                  | F   | 29  | 68            | 55                                | 23               | 0 65              | 0 03             | 0 60              | 0 60             | 9                      | 4                  | Considerable difficulty was experienced in collecting complete specimens, the amounts reported are taken from days when the specimens were complete |

TABLE 1  
*Exophthalmic goiter Group I*  
 Cases arranged in order of the initial basal metabolic rate

| Case number | Hospital record number | Sex | Age | Weight<br>kgm | Basal metabolic rate above normal |                  | Creatine          |                  | Creatinine        |                  | Creatinine coefficient | Days before effect | Remarks   |
|-------------|------------------------|-----|-----|---------------|-----------------------------------|------------------|-------------------|------------------|-------------------|------------------|------------------------|--------------------|---|
|             |                        |     |     |               | Before<br>Lugol's                 | After<br>Lugol's | Before<br>Lugol's | After<br>Lugol's | Before<br>Lugol's | After<br>Lugol's |                        |                    |   |
| 1           | 67755                  | F   | 31  | 62            | 90                                | 48               | 0.58              | 0.00             | 0.60              | 0.53             | 10                     | 7                  |   |
| 2*          | 169712                 | M   | 36  | 55            | 82                                | 26               | 1.51              | 0.09             | 1.15              | 0.91             | 21                     | 3                  |   |
| 3*          | 141738                 | M   | 35  | 49            | 79                                | 32               | 1.08              | 0.05             | 1.03              | 0.75             | 21                     | 7                  |   |
| 4           | 71191                  | F   | 17  | 46            | 79                                | 62               | 0.25              | 0.00             | 0.40              | 0.45             | 9                      | 8                  |   |
| 5           | 70682                  | F   | 22  | 57            | 71                                | 15               | 0.65              | 0.03             | 0.60              | 0.60             | 11                     | 6                  |   |
| 6           | 67955                  | F   | 38  | 53            | 65                                | 15               | 0.43              | 0.00             | 0.80              | 0.90             | 15                     | 4                  |   |
| 7           | 67911                  | F   | 31  | 59            | 65                                | 15               | 0.50              | 0.00             | 0.60              | 0.70             | 10                     | 3                  |   |
| 8*          | 172491                 | F   | 21  | 57            | 62                                | 30               | 0.40              | 0.10             | 0.80              | 0.80             | 14                     | 7                  |   |
| 9           | 65916                  | M   | 37  | 50            | 62                                | 23               | 0.20              | 0.00             | 0.70              | 0.70             | 14                     | 3                  | Colored   |
| 10          | 67444                  | F   | 21  | 63            | 60                                | 15               | 0.70              | 0.05             | 0.90              | 0.80             | 14                     | 3                  |   |
| 11*         | 171003                 | F   | 26  | 52            | 58                                | 16               | 1.00              | 0.30             | 0.95              | 0.50             | 18                     | 5                  |   |
| 12          | 70353                  | F   | 32  | 59            | 58                                | 23               | 0.59              | 0.05             | 0.90              | 0.80             | 15                     | 6                  |   |
| 13          | 71150                  | M   | 42  | 62            | 56                                | 29               | 0.40              | 0.00             | 0.60              | 0.40             | 10                     | 3                  | Colored   |
| 14          | 68592                  | F   | 26  | 36            | 55                                | 30               | 0.55              | 0.03             | 0.60              | 0.60             | 17                     | 3                  | Colored   |
| 15          | 65566                  | F   | 27  | 43            | 55                                | 17               | 0.50              | 0.02             | 0.70              | 0.70             | 16                     | 3                  | The creatine excretion was quite irregular in this case until after iodine was started  |
| 16          | 68083                  | F   | 29  | 68            | 55                                | 23               | 0.65              | 0.03             | 0.60              | 0.60             | 9                      | 4                  | Considerable difficulty was experienced in collecting complete specimens, the amounts reported are taken from days when the specimens were complete |

TABLE 2  
*Toxic adenoma Group II*

| Case number | Hospital record number | Sex | Age | Weight | Basal metabolic rate above normal |               | Creatine       |               | Creatinine     |               | Creatinine coefficient | Days before effect | Remarks  |
|-------------|------------------------|-----|-----|--------|-----------------------------------|---------------|----------------|---------------|----------------|---------------|------------------------|--------------------|--|
|             |                        |     |     | kgm    | Before Lugol's                    | After Lugol's | Before Lugol's | After Lugol's | Before Lugol's | After Lugol's |                        |                    |  |
|             |                        |     |     |        | per cent                          | per cent      | grams          | grams         | grams          | grams         |                        |                    |  |
| 1           | 66857                  | F   | 54  | 50     | 60                                | 67            | 0 00           | 0 00          | 0 30           | 0 30          | ?                      |                    | Case unsatisfactory from metabolic standpoint Included to show there was no urinary creatine Creatine had decreased from 0.50 gram creatine before iodine was excreted   |
| 2*          | 167578                 | F   | 58  | 45     | 47                                | 25            | 0 18           | 0 05          | 0 60           | 0 60          | 13                     | ?                  |  |
| 3           | 68778                  | F   | 45  | 56     | 40                                | 0             | 0 05           | 0 50          | 0 70           | 0 70          | 13                     | ?                  |  |
| 4           | 67195                  | F   | 51  | 60     | 40                                | 35            | 0 10           | 0 05          | 0 60           | 0 60          | 10                     |                    | Patient received only 4 cc Lugol's altogether in first ten days of experiment. The creatinuria increased thereafter This patient had 2 cc of Lugol's for 16 consecutive days without effect on general condition |
| 5           | 70254                  | F   | 45  | 56     | 37                                | 37            | 0 50           | 0 00          | 0 80           | 0 80          | 14                     | 7                  |  |
| 6           | 67265                  | M   | 59  | 52     | 35                                | 25            | 0 05           | 0 05          | 0 81           | 0 80          | 15                     |                    |  |
| 7           | 67620                  | F   | 41  | 56     | 30                                | 15            | 0 20           | 0 00          | 0 90           | 0 89          | 16                     | ?                  | Seventeen days of iodine administration with only slight effect Creatinine was very irregular during course and probably due to incomplete specimens in part although this was never definitely established      |
| 8           | 71141                  | F   | 40  | 69     | 25                                | 21            | 0 15           | 0 05          | 0 95           | 0 90          | 14                     | ?                  |  |
| 9           | 54558                  | F   | 37  | 52     | 22                                | 22            | 0 20           | 0 05          | 0 70           | 0 80          | 13                     | ?                  |  |
| 10*         | 170541                 | F   | 38  | 60     | 18                                | 14            | 0 40           | 0 05          | 0 76           | 0 75          | 13                     | 5?                 |  |
| 11          | 69950                  | F   | 34  | 62     | 20                                | 8             | 0 05           | 0 03          | 0 90           | 0 90          | 15                     |                    |  |

\* Cases observed at Lane and Stanford University Hospitals, San Francisco, by D A C

TABLE 2  
*Toxic adenoma Group II*

| Case number | Hospital record number | Sex | Age | Weight<br>kgm | Basal metabolic rate above normal |                  | Creatine          |                  | Creatinine        |                  | Creatinine coefficient | Days before effect | Remarks   |
|-------------|------------------------|-----|-----|---------------|-----------------------------------|------------------|-------------------|------------------|-------------------|------------------|------------------------|--------------------|---|
|             |                        |     |     |               | Before<br>Lugol's                 | After<br>Lugol's | Before<br>Lugol's | After<br>Lugol's | Before<br>Lugol's | After<br>Lugol's |                        |                    |   |
| 1           | 66857                  | F   | 54  | 50            | 60                                | 67               | grams             | 0 00             | grams             | 0 30             | ?                      |                    | Case unsatisfactory from metabolic standpoint Included to show there was no urinary creatine Creatine had decreased from 0.50 gram creatine before iodine was excreted Patient received only 4 cc Lugol's altogether in first ten days of experiment. The creatinuria increased thereafter This patient had 2 cc of Lugol's for 16 consecutive days without effect on general condition |
| 2*          | 167578                 | F   | 58  | 45            | 47                                | 25               | 0 18              | 0 05             | 0 60              | 0 60             | 13                     | ?                  |   |
| 3           | 68778                  | F   | 45  | 56            | 40                                | 0                | 0 05              | 0 50             | 0 70              | 0 70             | 13                     | ?                  |   |
| 4           | 67195                  | F   | 51  | 60            | 40                                | 35               | 0 10              | 0 05             | 0 60              | 0 60             | 10                     |                    |   |
| 5           | 70254                  | F   | 45  | 56            | 37                                | 37               | 0 50              | 0 00             | 0 80              | 0 80             | 14                     | 7                  |   |
| 6           | 67265                  | M   | 59  | 52            | 35                                | 25               | 0 05              | 0 05             | 0 81              | 0 80             | 15                     |                    |   |
| 7           | 67620                  | F   | 41  | 56            | 30                                | 15               | 0 20              | 0 00             | 0 90              | 0 89             | 16                     | ?                  |   |
| 8           | 71141                  | F   | 40  | 69            | 25                                | 21               | 0 15              | 0 05             | 0 95              | 0 90             | 14                     | ?                  |   |
| 9           | 54558                  | F   | 37  | 52            | 22                                | 22               | 0 20              | 0 05             | 0 70              | 0 80             | 13                     | ?                  |   |
| 10*         | 170541                 | F   | 38  | 60            | 18                                | 14               | 0 40              | 0 05             | 0 76              | 0 75             | 13                     | 5?                 |   |
| 11          | 69950                  | F   | 34  | 62            | 20                                | 8                | 0 05              | 0 03             | 0 90              | 0 90             | 15                     |                    |   |

\* Cases observed at Lane and Stanford University Hospitals, San Francisco, by D A C



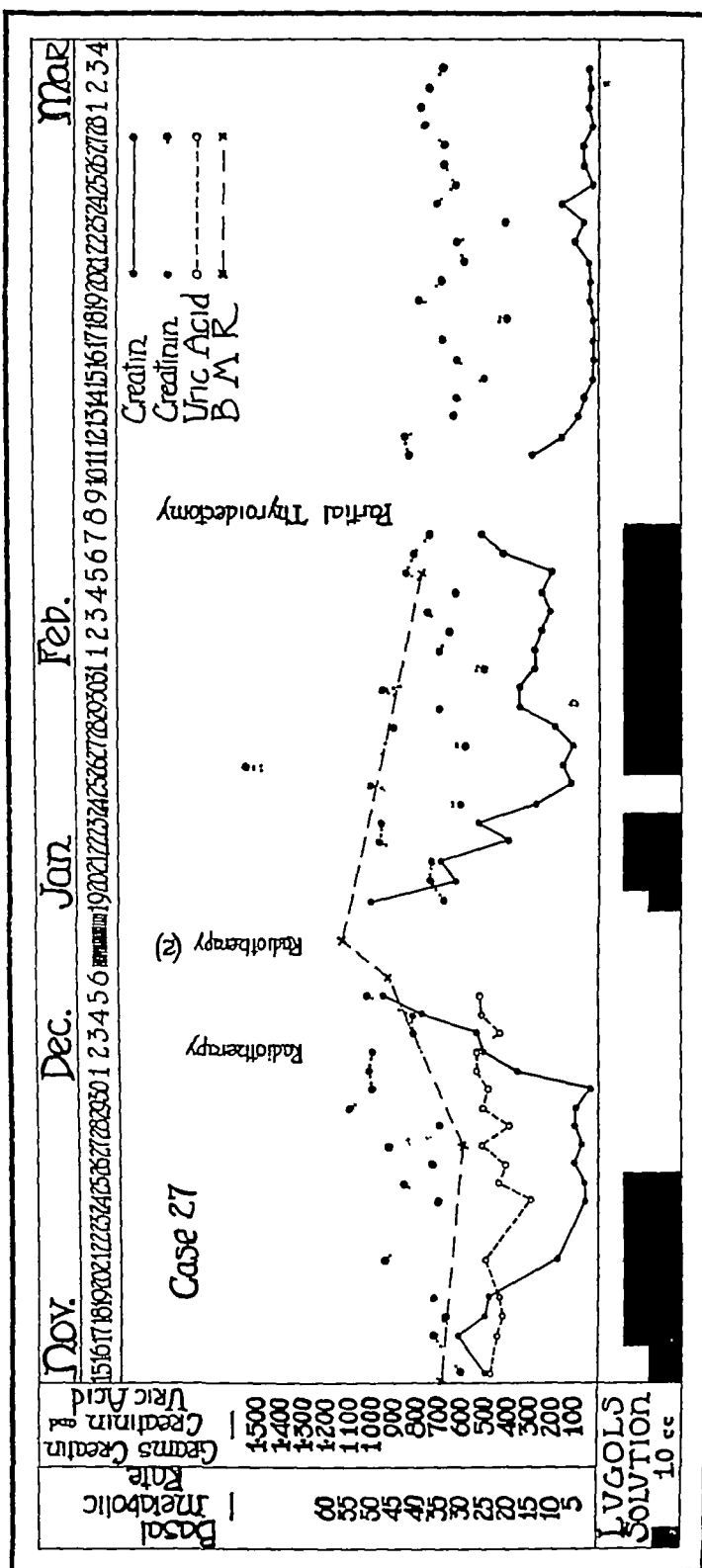


CHART 1 CASE 27 BETWEEN DECEMBER 6 AND JANUARY 7 THE PATIENT RECEIVED 2 CC LUGOL'S SOLUTION DAILY EXCEPT ONE WEEK BEFORE THE X-RAY TREATMENT ON DECEMBER 24

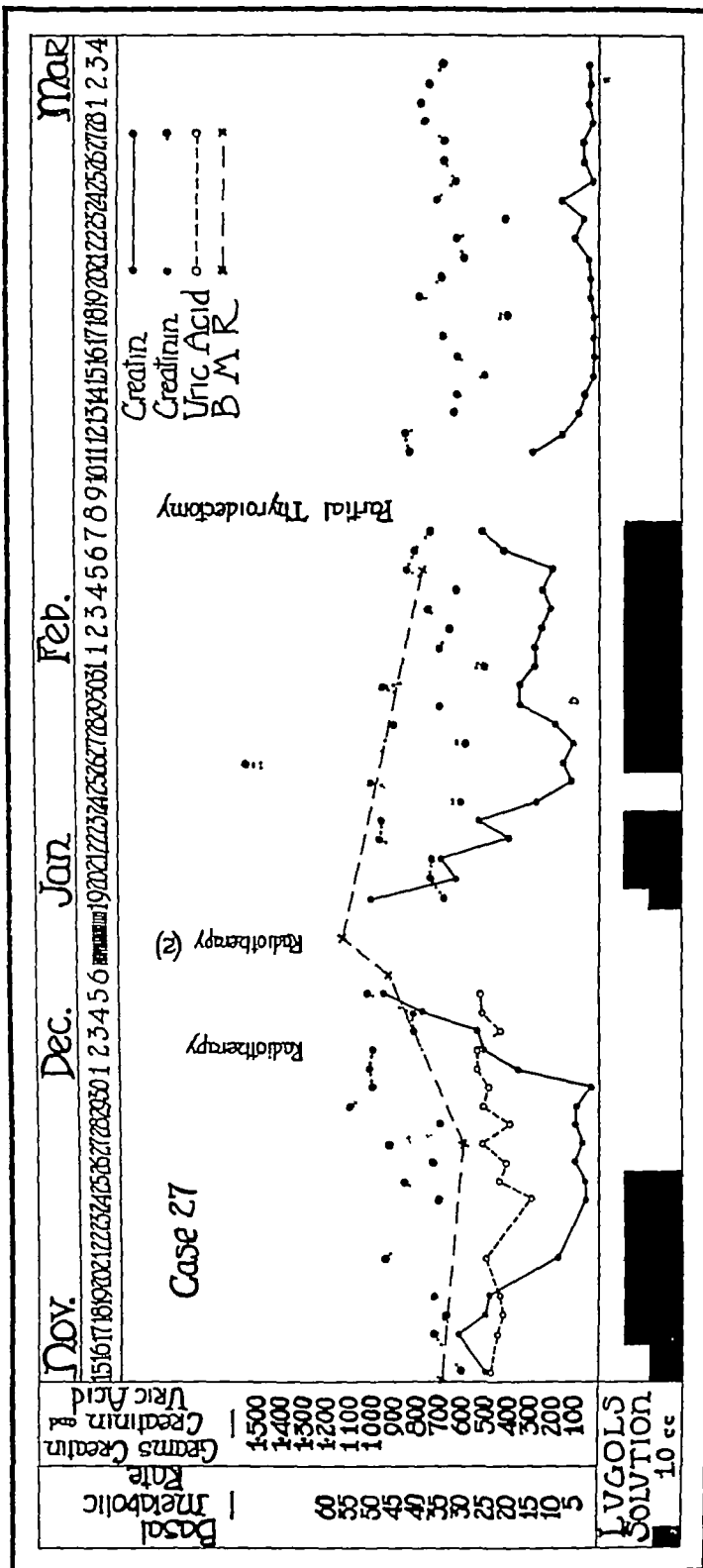


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from the urine Most of the clinical symptoms and metabolic disturbances in this disease are attributed to an increased amount of the active principle, thyroxine, circulating in the body The evidence for such a hypothesis is considerable Feeding thyroid gland or thyroxine to normal individuals and animals reproduces the symptoms and metabolic changes observed in the disease with the exception of exophthalmos In our experiments we were able to bring the subjects ill with exophthalmic goiter into nitrogen equilibrium without influencing greatly the creatinuria which is interesting in connection with Benedicts and Osterberg's (5) experiments with phlorizinized dogs which were given sufficient amounts of creatine-free protein to abolish the negative nitrogen balance without diminishing the excretion of creatine Following the administration of iodine there resulted a rapid diminution of the creatine in the urine to merely traces In a few instances this occurred without reduction of the basal metabolism, also a few cases with high basal rates excreted very little creatine with or without iodine As the latter phenomenon occurred most frequently in the group designated as "toxic adenomas" the question arises whether the pathological process in these cases differs in any way from the patients classified as exophthalmic goiter There is insufficient evidence at present to answer this question Certain it is that in those cases of hyperthyroidism with significant amounts of creatine in the urine there is marked diminution in the creatinuria following the intake of iodine It is difficult to separate this fact from the beneficial effect of iodine in general Marine suggests that the histological change in the hyperplastic thyroid gland brought about by iodine resulting as it does in distending the acini with colloid material, impairs the circulation in the vascular and lymphatic systems thereby preventing the escape of thyroxine into the general circulation This view would seem to be consistent with the evidence available at present Such being the case it would appear that thyroxine in abnormal amounts is directly associated with the appearance of creatine in the urine In support of this conception is the fact that both in men (6) and animals (7) creatinuria is produced by feeding either the thyroid gland or the actual principle Sturgis and associates (8) showed that the increased basal metabolism produced in rabbits by feeding thyroid extract was not lowered by the

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## THE VITAMIN B CONTENT OF CANCER

By HENRY JACKSON, JR., AND CLEMENT I. KRANTZ

*(From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University and the Thorndike Memorial Laboratory, Boston City Hospital)*

(Received for publication September 17, 1928)

Burrows (1) has been led to believe that cancer may be due to a local excess of vitamin B in the tissue and he and his co worker Jorstad bring forward some evidence that the Jensen rat sarcoma does actually contain an abnormally great amount of this accessory food substance (2) (3) They fed young rats a basic diet free from vitamin B to which were added ten grams Jensen rat sarcoma and from the growth curves obtained on this diet they conclude that cancerous tissue contains an abnormally great amount of vitamin B No normal resting organ was, however, directly contrasted with the malignant tissue, so we are left in doubt as to the exact quantitative differences in vitamin B content between normal and neoplastic tissue If cancer really be due to, or associated with, an increase of vitamin B, then actively growing neoplastic tissue should, as Burrows claims, contain more of this accessory food factor than normal tissue Experiments were therefore devised to check the results of Burrows and Jorstad as the matter is not without both theoretical and practical importance

Young white rats were placed on a basic diet containing

|              | per cent |
|--------------|----------|
| Casein       | 18       |
| Starch       | 54       |
| Butter fat   | 24       |
| Salt mixture | 4        |

The salt mixture was that described by Osborne and Mendel (4) All ingredients were free from vitamin B Each rat was kept in a separate cage and adequate precautions were taken against the consumption of feces Tap water was given freely at all times Each rat was weighed every two days. The basic vitamin B free diet was renewed daily In addition to the basic diet each rat received in a separate

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Ten rats were fed human cancer, twelve were fed mouse cancer, six normal mouse liver, and four were placed on pure diets without addition of tissue (chart 1)

An examination of chart 1 shows that even 500 mgm dried human cancer per diem was insufficient to produce adequate growth. After a

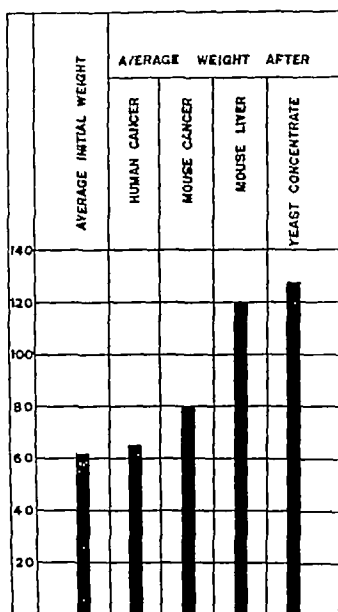


CHART 2 AVERAGE WEIGHTS AT THE BEGINNING OF THE EXPERIMENT AND AT THE END OF THE FEEDING PERIODS ON VARIOUS DIETS

preliminary increase in the weight of the animals presumably due to stored vitamin B there was in all instances a prompt and rapid fall in weight. This rise and fall will further be seen to be virtually independent of the amount of tissue fed—in this instance a rapidly growing carcinoma of the kidney removed at operation. The tumor was com-

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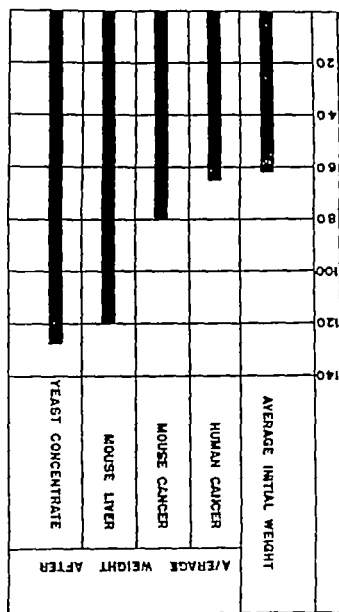


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# STUDIES ON DIGITALIS IN AMBULATORY CARDIAC PATIENTS

## II THE ELIMINATION OF DIGITALIS IN MAN

BY HARRY GOLD AND ARTHUR C DEGRAFF

*(From the Third Medical (New York University) Division of Bellevue Hospital and Department of Pharmacology of Cornell University Medical College)*

(Received for publication September 14, 1928)

A study of the rate of elimination of digitalis in normal animals in terms of persistence of action was published by one of us (1) in 1923. The curves invariably show that after a single large injection, elimination is very rapid at first and then slower, i.e., as the quantity of digitalis in the body diminishes, that eliminated daily also diminishes. This was demonstrated in another way as seen from the following example taken from that paper: each of several animals received a single intravenous injection of 75 per cent of the average fatal dose of a given tincture of digitalis. In 24 hours, the average quantity eliminated was 45 per cent of a fatal dose. If the capacity for elimination of the drug could be expressed as a fixed quantity per day—45 per cent of a fatal dose for this specimen—an animal receiving a daily intravenous injection of 50 per cent of a fatal dose of this tincture would require about 20 such daily doses to cause death, and an animal receiving a daily injection of 25 per cent of a fatal dose of this specimen would never accumulate sufficient digitalis in the body to cause death. As a matter of fact, two animals that had received daily injections of 50 per cent of a fatal dose of this tincture died after the fourth and fifth dose, respectively, and two animals that had received daily injections of 25 per cent of a fatal dose died after the tenth and eleventh injection respectively. The conclusion necessarily follows that the amount of digitalis eliminated daily depends upon the amount of the drug in the body, and that in all probability, only a percentage of that present can be eliminated in a unit of time.

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ism and with the evidence obtained from animal experiments concerning digitalis elimination, caused us to question the adequacy of the method employed to determine the daily rate of disappearance of digitalis in man. A number of experiments carried out in the clinic appears to us to leave little doubt that in essentials, man does not differ from other animals in the elimination of digitalis. They show that the *daily excretion dose is a misconception, that the amount of digitalis eliminated in a day cannot be stated as a given quantity under all conditions, but varies with the amount of the drug present in the body*. These experiments are the subject of the present report.

The studies have been carried out upon ambulatory cardiac patients with auricular fibrillation, because in these the onset and disappearance of digitalis effects can be established with greater precision. The type of medical and social service organization of this clinic<sup>1</sup> and the personal contact established between the patients and the staff, have made it possible to carry out observations over long periods of time with results as reliable, within limits, as those carried out on a hospital ward in this type of work. Patients who could not be depended upon to comply strictly with orders were excluded from the study. Digitalis was employed in a manner similar to that described in a previous paper (6). Compressed tablets of dried digitalis leaf standardized by the cat unit method, were dispensed to the patients and the daily amount ordered to be taken in a single dose.

The ventricular rate was used to indicate the intensity of digitalis action and this was particularly satisfactory in that group of patients who are in this respect very sensitive to the drug, in whom marked changes in the ventricular rate occur readily when the drug is given or withheld. In all instances the work and exercise during a given period were inquired about so as to exclude those cases in which it could not be stated with a fair degree of certainty that there was neither more exertion nor more rest to account for the changes in the rate attributed to the withdrawal or administration of digitalis. The apex rate was counted by the stethoscope under fairly uniform conditions with the patient sitting or lying after a period of rest. With these precautions, the occasional variability is far less striking than the general uniformity

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Patient E. P. (chart 1) appeared at the clinic with a ventricular rate of 164, he had never had any digitalis. He was permitted to go one week longer without the drug and the rate remained unchanged. He was then given 0.2 gram daily of specimen "A". The rate gradually decreased, reached a level of about 80 by the third week, and remained constant during a subsequent period of observation of six weeks during which the same dose was taken. Several months later, this patient was under the influence of digitalis and the ventricular rate was 64. The drug was withheld for a period of three weeks and the ventricular rate increased to 136. He was then given 0.2 gram daily of specimen "D". The ventricular rate again diminished gradually and reached a level of about 80, at which it remained for several weeks with the same daily dose of the drug. This was repeated at a subsequent time with specimen "C".

Since progressively increasing intensity of the digitalis effect mentioned (depression of conduction) during the administration of a fixed daily dose of the drug is taken as evidence that the patient is receiving more digitalis than he is eliminating, it must be assumed that when this patient had no digitalis in the body, he was incapable of eliminating the 0.2 gram that was given daily, but after he had accumulated a certain portion of the 4.2 grams that had been given in a period of twenty-one days, he now was eliminating 0.2 gram daily.

It is also interesting to note that the curves are essentially similar with specimens "A" and "D" which are very similar in activity, the former 79 mgm, the latter 87 mgm to the cat unit. With specimen "C" it took more time to accumulate sufficient digitalis to produce the results as might have been anticipated from the fact that it was a poor specimen with an activity of 140 mgm to the cat unit.

In patient J. R. (chart 2), after digitalis had been given for several months, the drug was withheld and the ventricular rate gradually increased during a period of twelve weeks to 120. The patient then received 0.2 gram daily of specimen "D" and the rate gradually diminished until it reached a level that was maintained for several weeks. The dose was increased to 0.25 gram daily for fourteen weeks (98 doses) and the rate remained unchanged. This indicates that a patient who was able to eliminate 0.25 gram daily after considerable digitalis had accumulated, was unable to eliminate even 0.2 gram daily.

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TABLE 1

*Showing the clinical classification of the patients used for the tests that are summarized in table 2*

| Number of patient | Sex | Age | Weight<br>kgm. | Diagnosis        |  | Functional classification |
|-------------------|-----|-----|----------------|------------------|--|---------------------------|
|                   |     |     |                | Etiological      | Anatomical   |                           |
| 994               | M   | 27  | 65 9           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency aortic stenosis and insufficiency  | II-a                      |
| 1261              | M   | 39  | 70 9           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 65                | M   | 56  | 66 3           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency | III                       |
| 1119              | M   | 58  | 100            | Unknown          | Enlarged heart   | II b                      |
| 1254              | M   | 48  | 67 2           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1369              | M   | 58  | 98 6           | Arteriosclerotic | Enlarged heart   | II-b                      |
| 1388              | M   | 67  | 60 0           | Arteriosclerotic | Enlarged heart   | II b                      |
| 1715              | F   | 51  | 50 0           | Arteriosclerotic | Enlarged heart   | II-b                      |
| 124               | F   | 35  | 63 6           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 594               | F   | 58  | 61 8           | Arteriosclerotic | Enlarged heart   | II b                      |
| 1768              | M   | 35  | 61 3           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1181              | M   | 54  | 62 2           | Unknown          | Enlarged heart   | II b                      |
| 948               | M   | 18  | 40 9           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency, adhesive pericarditis             | II b                      |
| 1519              | F   | 38  | 70 0           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II-b                      |
| 1201              | M   | 46  | 70 4           | Unknown          | Enlarged heart   | II-a                      |
| 629               | M   | 51  | 71 3           | Unknown          | Enlarged heart, mitral stenosis and insufficiency                                    | II-a                      |
| 1848              | F   | 36  | 60 0           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1858              | F   | 38  | 60 0           | Unknown          | Enlarged heart   | II b                      |
| 1728              | F   | 60  | 83 6           | Unknown          | Enlarged heart   | II b                      |
| 679               | M   | 32  | 55 9           | Unknown          | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1892              | F   | 36  | 52 7           | Unknown          | Enlarged heart   | II b                      |
| 1855              | F   | 41  | 90 9           | Unknown          | Enlarged heart mitral stenosis and insufficiency                                     | II b                      |
| 1615              | M   | 67  | 86 3           | Arteriosclerotic | Enlarged heart, aortitis   | II-a                      |

\* (II a) able to carry on slightly diminished physical activity (II b) able to carry on greatly diminished physical activity (III) symptoms of heart failure at rest

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| 1119              | M   | 58  | 100            | Unknown          | Enlarged heart   | II b                      |
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| 1369              | M   | 58  | 98 6           | Arteriosclerotic | Enlarged heart   | II-b                      |
| 1388              | M   | 67  | 60 0           | Arteriosclerotic | Enlarged heart   | II b                      |
| 1715              | F   | 51  | 50 0           | Arteriosclerotic | Enlarged heart   | II-b                      |
| 124               | F   | 35  | 63 6           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 594               | F   | 58  | 61 8           | Arteriosclerotic | Enlarged heart   | II b                      |
| 1768              | M   | 35  | 61 3           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1181              | M   | 54  | 62 2           | Unknown          | Enlarged heart   | II b                      |
| 948               | M   | 18  | 40 9           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency, adhesive pericarditis             | II b                      |
| 1519              | F   | 38  | 70 0           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II-b                      |
| 1201              | M   | 46  | 70 4           | Unknown          | Enlarged heart   | II-a                      |
| 629               | M   | 51  | 71 3           | Unknown          | Enlarged heart, mitral stenosis and insufficiency                                    | II-a                      |
| 1848              | F   | 36  | 60 0           | Rheumatic        | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1858              | F   | 38  | 60 0           | Unknown          | Enlarged heart   | II b                      |
| 1728              | F   | 60  | 83 6           | Unknown          | Enlarged heart   | II b                      |
| 679               | M   | 32  | 55 9           | Unknown          | Enlarged heart, mitral stenosis and insufficiency                                    | II b                      |
| 1892              | F   | 36  | 52 7           | Unknown          | Enlarged heart   | II b                      |
| 1855              | F   | 41  | 90 9           | Unknown          | Enlarged heart mitral stenosis and insufficiency                                     | II b                      |
| 1615              | M   | 67  | 86 3           | Arteriosclerotic | Enlarged heart, aortitis   | II-a                      |

\* (II a) able to carry on slightly diminished physical activity (II b) able to carry on greatly diminished physical activity (III) symptoms of heart failure at rest

TABLE 2—Continued

| Number of patient | Number of test and specimen of digitalis | Daily dose   | Number of days | Ventricular rate |
|-------------------|--|--------------|----------------|------------------|
|                   |  | <i>grams</i> |                |                  |
| 56                | 1 A                                      | 0            | 14             | 126              |
|                   |  | 0 2          | 7              | 84               |
|                   |  | 0 2          | 14             | 86               |
|                   |  | 0 25         | 7              | 84               |
|                   |  | 0 25         | 14             | 84               |
|                   |  | 0 25         | 14             | 78               |
|                   |  | 0 25         | 14             | 80               |
|                   |  | 0 25         | 14             | 82               |
|                   |  | 0 4          | 14             | 70               |
|                   | 2 C                                      | 0            | 7              | 96               |
|                   |  | 0 2          | 21             | 72               |
|                   |  | 0 2          | 28             | 66               |
|                   |  | 0 2          | 28             | 66               |
|                   |  | 0 2          | 28             | 66               |
|                   |  | 0 2          | 28             | 64               |
|                   |  | 0 2          | 28             | 66               |
|                   | 3-E                                      | 0            | 21             | 100              |
|                   |  | 0 13         | 28             | 82               |
|                   |  | 0 13         | 14             | 82               |
|                   |  | 0 13         | 21             | 80               |
|                   |  | 0 13         | 21             | 78               |
|                   | 4-E                                      | 0            | 28             | 120              |
|                   |  | 0 2          | 14             | 92               |
|                   |  | 0 13         | 21             | 74               |
|                   |  | 0 13         | 21             | 76               |
|                   |  | 0 13         | 14             | 84               |
|                   |  | 0 13         | 28             | 90               |
| 1119              | 1 C                                      | 0            | 14             | 112              |
|                   |  | 0 2          | 7              | 90               |
|                   |  | 0 2          | 7              | 78               |
|                   |  | 0 2          | 7              | 74               |
|                   |  | 0 2          | 14             | 74               |
|                   |  | 0 2          | 21             | 72               |
|                   |  | 0 13         | 14             | 74               |
|                   |  | 0 13         | 21             | 70               |
|                   | 2 D                                      | 0            | 35             | 130              |
|                   |  | 0 2          | 7              | 104              |
|                   |  | 0 2          | 14             | 94               |
|                   |  | 0 2          | 28             | 78               |
|                   |  | 0 2          | 28             | 88               |
|                   |  | 0 2          | 28             | 80               |
|                   |  | 0 2          | 28             | 88               |

TABLE 2—Continued

| Number of patient | Number of test and specimen of digitalis | Daily dose   | Number of days | Ventricular rate |
|-------------------|--|--------------|----------------|------------------|
|                   |  | <i>grams</i> |                |                  |
| 56                | 1 A                                      | 0            | 14             | 126              |
|                   |  | 0 2          | 7              | 84               |
|                   |  | 0 2          | 14             | 86               |
|                   |  | 0 25         | 7              | 84               |
|                   |  | 0 25         | 14             | 84               |
|                   |  | 0 25         | 14             | 78               |
|                   |  | 0 25         | 14             | 80               |
|                   |  | 0 25         | 14             | 82               |
|                   |  | 0 4          | 14             | 70               |
|                   | 2 C                                      | 0            | 7              | 96               |
|                   |  | 0 2          | 21             | 72               |
|                   |  | 0 2          | 28             | 66               |
|                   |  | 0 2          | 28             | 66               |
|                   |  | 0 2          | 28             | 66               |
|                   |  | 0 2          | 28             | 64               |
|                   |  | 0 2          | 28             | 66               |
|                   | 3-E                                      | 0            | 21             | 100              |
|                   |  | 0 13         | 28             | 82               |
|                   |  | 0 13         | 14             | 82               |
|                   |  | 0 13         | 21             | 80               |
|                   |  | 0 13         | 21             | 78               |
|                   | 4-E                                      | 0            | 28             | 120              |
|                   |  | 0 2          | 14             | 92               |
|                   |  | 0 13         | 21             | 74               |
|                   |  | 0 13         | 21             | 76               |
|                   |  | 0 13         | 14             | 84               |
|                   |  | 0 13         | 28             | 90               |
| 1119              | 1 C                                      | 0            | 14             | 112              |
|                   |  | 0 2          | 7              | 90               |
|                   |  | 0 2          | 7              | 78               |
|                   |  | 0 2          | 7              | 74               |
|                   |  | 0 2          | 14             | 74               |
|                   |  | 0 2          | 21             | 72               |
|                   |  | 0 13         | 14             | 74               |
|                   |  | 0 13         | 21             | 70               |
|                   | 2 D                                      | 0            | 35             | 130              |
|                   |  | 0 2          | 7              | 104              |
|                   |  | 0 2          | 14             | 94               |
|                   |  | 0 2          | 28             | 78               |
|                   |  | 0 2          | 28             | 88               |
|                   |  | 0 2          | 28             | 80               |
|                   |  | 0 2          | 28             | 88               |

TABLE 2—Continued

| Number of patient | Number of test and specimen of digitalis | Daily dose   | Number of days | Ventricular rate |
|-------------------|--|--------------|----------------|------------------|
|                   |  | <i>grams</i> |                |                  |
| 1768              | 1 E                                      | 0            | 77             | 120              |
|                   |  | 0 16         | 7              | 80               |
|                   |  | 0 16         | 7              | 80               |
|                   |  | 0 16         | 7              | 78               |
|                   |  | 0 16         | 3              |                  |
|                   |  | 0            | 4              | 78               |
|                   |  | 0            | 14             | 78               |
|                   |  | 0 16         | 14             | 78               |
| 1181              | 1-C                                      | 0            | 35             | 92               |
|                   |  | 0 2          | 14             | 66               |
|                   |  | 0 2          | 14             | 56               |
|                   |  | 0 2          | 21             | 68               |
|                   |  | 0 2          | 21             | 58               |
|                   | 2 D                                      | 0            | 42             | 100              |
|                   |  | 0 2          | 14             | 54               |
|                   |  | 0 2          | 14             | 68               |
|                   |  | 0 2          | 21             | 60               |
|                   |  | 0 2          | 21             | 58               |
| 948               | 1 A                                      | 0            | months         | 200              |
|                   |  | 0 2          | 7              | 98               |
|                   |  | 0 13         | 7              | 96               |
|                   |  | 0 2          | 7              | 70               |
|                   |  | 0 2          | 7              | 86               |
|                   |  | 0 2          | 7              | 76               |
|                   |  | 0 2          | 7              | 80               |
|                   |  | 0 2          | 7              | 76               |
|                   |  |              |                |                  |
| 1519              | 1 E                                      | 0            | 7              | 120              |
|                   |  | 0 13         | 14             | 92               |
|                   |  | 0 13         | 21             | 100              |
|                   |  | 0 13         | 14             | 82               |
|                   |  | 0 2          | 14             | 84               |
|                   |  | 0 2          | 7              | 82               |
|                   |  | 0 2          | 7              | 84               |
|                   |  | 0 2          | 28             | 82               |
|                   |  |              |                |                  |
| 1201              | 1 D                                      | 0            | 133            | 160              |
|                   |  | 0 25         | 7              | 88               |
|                   |  | 0 2          | 14             | 78               |
|                   |  | 0 2          | 21             | 64               |
|                   |  | 0 2          | 7              | 66               |
|                   |  | 0 2          | 14             | 65               |

TABLE 2—Continued

| Number of patient | Number of test and specimen of digitalis | Daily dose   | Number of days | Ventricular rate |
|-------------------|--|--------------|----------------|------------------|
|                   |  | <i>grams</i> |                |                  |
| 1768              | 1 E                                      | 0            | 77             | 120              |
|                   |  | 0 16         | 7              | 80               |
|                   |  | 0 16         | 7              | 80               |
|                   |  | 0 16         | 7              | 78               |
|                   |  | 0 16         | 3              |                  |
|                   |  | 0            | 4              | 78               |
|                   |  | 0            | 14             | 78               |
|                   |  | 0 16         | 14             | 78               |
| 1181              | 1-C                                      | 0            | 35             | 92               |
|                   |  | 0 2          | 14             | 66               |
|                   |  | 0 2          | 14             | 56               |
|                   |  | 0 2          | 21             | 68               |
|                   |  | 0 2          | 21             | 58               |
|                   | 2 D                                      | 0            | 42             | 100              |
|                   |  | 0 2          | 14             | 54               |
|                   |  | 0 2          | 14             | 68               |
|                   |  | 0 2          | 21             | 60               |
| 948               | 1 A                                      | 0 2          | 21             | 58               |
|                   |  | 0            | months         | 200              |
|                   |  | 0 2          | 7              | 98               |
|                   |  | 0 13         | 7              | 96               |
|                   |  | 0 2          | 7              | 70               |
|                   |  | 0 2          | 7              | 86               |
|                   |  | 0 2          | 7              | 76               |
|                   |  | 0 2          | 7              | 80               |
| 1519              | 1 E                                      | 0 2          | 7              | 76               |
|                   |  | 0            | 7              | 120              |
|                   |  | 0 13         | 14             | 92               |
|                   |  | 0 13         | 21             | 100              |
|                   |  | 0 13         | 14             | 82               |
|                   |  | 0 2          | 14             | 84               |
|                   |  | 0 2          | 7              | 82               |
|                   |  | 0 2          | 7              | 84               |
| 1201              | 1 D                                      | 0 2          | 28             | 82               |
|                   |  | 0            | 133            | 160              |
|                   |  | 0 25         | 7              | 88               |
|                   |  | 0 2          | 14             | 78               |
|                   |  | 0 2          | 21             | 64               |
|                   |  | 0 2          | 7              | 66               |
|                   |  | 0 2          | 14             | 65               |

TABLE 2—*Continued*

| Number of patient | Number of test and specimen of digitalis | Daily dose                  | Number of days | Ventricular rate |
|-------------------|--|-----------------------------|----------------|------------------|
|                   |  | <i>grams</i>                |                |                  |
| 679               | 3-F                                      | —                           | —              | 120              |
|                   |  | 0.2                         | 7              | 102              |
|                   |  | 0.2                         | 7              | 94               |
|                   |  | 0.2                         | 21             | 103              |
|                   |  | 0.3                         | 14             | 86               |
|                   |  | 0.3                         | 14             | 72               |
|                   |  | 0.3                         | 21             | 64               |
|                   |  | 0.3                         | 21             | 80               |
|                   |  | 0.3                         | 21             | 76               |
|                   |  | 0.3                         | 21             | 80               |
|                   |  | 0.3                         | 21             | 78               |
| 1892              | 1 F                                      | Tincture taken occasionally |                | 132              |
|                   |  | 0.2                         | 7              | 100              |
|                   |  | 0.2                         | 7              | 81               |
|                   |  | 0.2                         | 7              | 86               |
|                   |  | 0.2                         | 7              | 86               |
| 1855              | 1 F                                      | 0                           | 14             | 100              |
|                   |  | 0.1                         | 7              | 83               |
|                   |  | 0.1                         | 7              | 71               |
|                   |  | 0.1                         | 7              | 76               |
|                   |  | 0.1                         | 7              | 67               |
|                   |  | 0.1                         | 21             | 70               |
|                   |  | 0.1                         | 21             | 62               |
|                   |  | 0.1                         | 21             | 57               |
|                   |  | 0.1                         | 21             | 75               |
| 1615              | 1 F                                      | 0.2                         | 29†            | 72†              |
|                   |  | 0                           | 7              | 72               |
|                   |  | 0                           | 14             | 106              |
|                   |  | 0                           | 7              | 110              |
|                   |  | 0                           | 7              | 99               |
|                   |  | 0.13*                       | 7              | 126              |
|                   |  | 0.2                         | 7              | 106              |
|                   |  | 0.2                         | 14             | 86               |
|                   |  | 0.2                         | 21             | 68               |
|                   |  | 0.2                         | 14             | 76               |
|                   |  | 0.2                         | 21             | 74               |
|                   |  | 0.2                         | 21             | 74               |

\* Specimen E

† Average of 11 records.

TABLE 2—*Continued*

| Number of patient | Number of test and specimen of digitalis | Daily dose                  | Number of days | Ventricular rate |
|-------------------|--|-----------------------------|----------------|------------------|
|                   |  | <i>grams</i>                |                |                  |
| 679               | 3-F                                      | —                           | —              | 120              |
|                   |  | 0.2                         | 7              | 102              |
|                   |  | 0.2                         | 7              | 94               |
|                   |  | 0.2                         | 21             | 103              |
|                   |  | 0.3                         | 14             | 86               |
|                   |  | 0.3                         | 14             | 72               |
|                   |  | 0.3                         | 21             | 64               |
|                   |  | 0.3                         | 21             | 80               |
|                   |  | 0.3                         | 21             | 76               |
|                   |  | 0.3                         | 21             | 80               |
|                   |  | 0.3                         | 21             | 78               |
| 1892              | 1 F                                      | Tincture taken occasionally |                | 132              |
|                   |  | 0.2                         | 7              | 100              |
|                   |  | 0.2                         | 7              | 81               |
|                   |  | 0.2                         | 7              | 86               |
|                   |  | 0.2                         | 7              | 86               |
| 1855              | 1 F                                      | 0                           | 14             | 100              |
|                   |  | 0.1                         | 7              | 83               |
|                   |  | 0.1                         | 7              | 71               |
|                   |  | 0.1                         | 7              | 76               |
|                   |  | 0.1                         | 7              | 67               |
|                   |  | 0.1                         | 21             | 70               |
|                   |  | 0.1                         | 21             | 62               |
|                   |  | 0.1                         | 21             | 57               |
|                   |  | 0.1                         | 21             | 75               |
| 1615              | 1 F                                      | 0.2                         | 294            | 72†              |
|                   |  | 0                           | 7              | 72               |
|                   |  | 0                           | 14             | 106              |
|                   |  | 0                           | 7              | 110              |
|                   |  | 0                           | 7              | 99               |
|                   |  | 0.13*                       | 7              | 126              |
|                   |  | 0.2                         | 7              | 106              |
|                   |  | 0.2                         | 14             | 86               |
|                   |  | 0.2                         | 21             | 68               |
|                   |  | 0.2                         | 14             | 76               |
|                   |  | 0.2                         | 21             | 74               |
|                   |  | 0.2                         | 21             | 74               |

\* Specimen E

† Average of 11 records.



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